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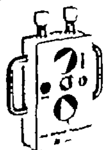
Pacemaking in the treatment of heart block provides palliation of symptoms *and* prolongation of survival



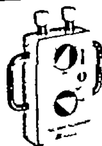
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(MODEL 5841)
ADJUSTABLE RATE



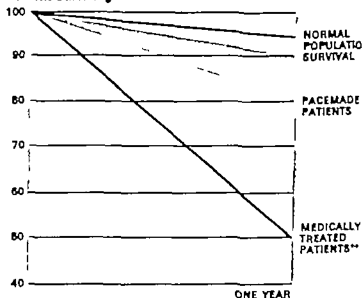
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(After Chardack W M Cardiac Pacemakers and Heart Block in Gibbon J H Surgery of the Chest Philadelphia W B Saunders Co 1969 pp 824-865)

Morris J J J Whalen R E McIntosh, H D Thompson, H K Brown, I W J nd Young W G Permanent Ventricular Pacemakers A Compa son of Transthoracic nd Transvenous Imple tation, *Circulation* 36 587 1967

Sykosch, J B hner M nd Eff rt, S ech Jahre Schrittmachertherapie *Deutsche Med Wschr* 93 777 1968

**Curd G W J Dennis E W Jordan J McN mara, D Montero, A C Peterson, P K Pruitt, R D and Schnu S Etiology of Atrioventricular H art Bl k A Study f its Relevance to Prognosis and Pacemake Ther py *Cardiovasc Res Cent Bull* 1 63 1963

Friedberg, C K Donoso E nd Stei W G Nonsurgical Acq ired H rt Block *Ann NY Acad Sci* 111 835 1964

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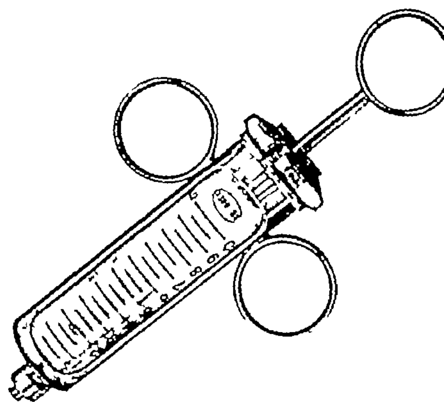
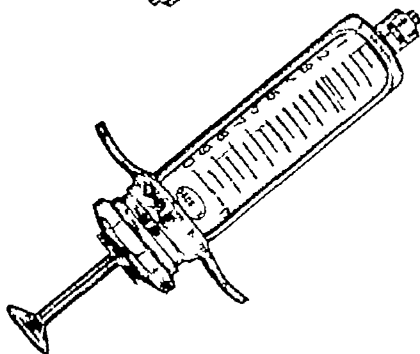
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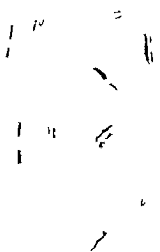
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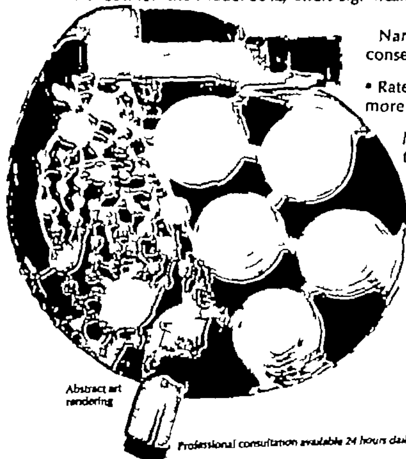
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Editorial

The integration of the cardiovascular response to diving

Lloyd R. Yonce
*Björn Folkow**
Chapel Hill, N. C.

Sufficient evidence has now accumulated to present a reasonably accurate integrated picture of the cardiovascular adjustments to water submersion in "diving" animals, especially the seal and duck. Many of the manifestations of this response are also seen in some nondiving animals, including man, but to a much less degree. The most obvious and perhaps the most widely studied responses are the bradycardia and the cessation of respiration. These were first recorded in the classical studies by Bert,[1] using the duck as an experimental animal. It was not until 1934 that Irving[2] suggested the bradycardia occurring during submersion forms part of a widespread and profound reflex adjustment of the cardiovascular system so organized that the oxygen reserves present in the blood and the respiratory system are preferentially distributed to the essential organs, the brain and the heart. Some of the subsequent experimental data on ducks that support Irving's hypothesis will be discussed.

The mean control heart rate of the duck in the laboratory conditions was 244 beats per minute (SD ± 63).[3] When the head of the duck was submerged, the heart rate immediately decreased to 80 to 90 per cent of the control value.[4] In some animals, as in the seal, the heart rate may precipitously fall to 10 per cent of the control value.[4] This immediate reflex response is mediated primarily by the vagal efferent fibers to the heart. The nature of the sensory stimulation that produces the bradycardia is not well understood but is presumed to originate in the nasal area since immersion of the nares and an intact trigeminal nerve are necessary to produce the bradycardia.[5] Initiation of the response does not appear to be related to pressure, temperature, or osmotic receptors. Visual perception is also not necessary since blindfolded ducks respond equally well or better to submersion. However, other somatic receptor sites than the nasal area are probably involved.[7] The modality of the sensory receptors responsible for the initiation of the diving response needs additional investigation.

Following the initial decreased heart rate, continued submersion of the duck results in a progressive increase in bradycardia down to values of 10 to 20 beats per minute. This intensive bradycardia appears dependent on the gradually developing hypercapnia and hypoxia during the submersion, implying a stimulation of the chemoreceptors and perhaps a direct stimulation of central nervous system centers.

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*Address: Physiology Department, University of Göteborg, Göteborg, Sweden.

Editors' note. Because of the ever increasing interest in submarine medicine and in industrial and naval developments under the sea, [illegible] realized that cardiovascular and submarine medicine will be ever increasing in importance. [illegible] of this, this editorial should be of interest to our readers who in the future will be concerned with submarine cardiology.

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Hypercapnia seems to exert a stronger influence then hypoxia [1,4] Daly and Scott[5,9] have shown in dogs that chemoreceptor activation results in a decreased heart rate and vasoconstriction in muscle skin and intestine if the simultaneously induced reflex increase in respiration is avoided These same general effects are seen during a dive where respiration has essentially stopped It would appear that some evolutionary development has occurred in nondiving animals to counteract hypercapnic or hypoxic conditions by increasing respiration In diving animals the chemoreceptor activation works to conserve the oxygen stored at the time of the dive primarily for the brain and heart. Comparatively the chemoreceptor induced reflex in diving animals is probably phylogenetically older than the reflex response in nondiving animals.

There has been little doubt that the intense bradycardia associated with submersion must be accompanied by a decreased cardiac output However only recently have data been obtained providing some quantitation Elsner [10] in a limited study stated Cardiac output varied in close accordance with the heart rate Shelton and Jones[11] found a decreased stroke volume as well as a decreased cardiac output in diving frogs Murdaugh and associates[12] demonstrated that cardiac output decreased to 6 to 36 per cent (mean 12 per cent) of the predive value in seals. There was no consistent change in the stroke volume.

Folkow Nilsson and Yonce[3] using ducks found a decreased cardiac output and stroke volume The mean resting cardiac output was 1 509 ml per minute (S D 245) for the predive control period[8] The heart weight was 15 to 21 grams a size comparable with a cat which has a resting cardiac output of only about 600 ml per minute These data are in agreement with the previous findings by Folkow Fuxe and Sonnenschein[13] that resting muscle blood flow is usually three to four times that in the cat under similar experimental conditions. Also the maximal flow capacity to the muscles is nearly three times higher in the duck Since the A V oxygen difference in ducks is not different from nondiving animals (Folkow and Yonce, unpublished results) the high blood flow will maintain an oxygen reserve in the venous blood in the face of the high metabolic rate. With larger blood volume per kilogram weight, the duck has a reservoir of oxygen to use for the brain and heart during a dive.

The cardiac output during the dive usually decreased to values below 100 ml per minute The computed stroke volume nearly always decreased in spite of an increased central venous pressure. The increased filling pressure coupled with the observation by Aakhus and Johansen[14] that the heart increases in size during a dive led to the hypothesis that the decreased stroke volume was a result of vagal inhibition of the ventricle Additional investigations substantiated that vagal stimulation has a negative inotropic effect on the ventricle of the duck [15] The resulting decreased amount of work that the heart does during the dive reduces the oxygen demand of the myocardium for the oxygen stores. These data are consistent with the results of DeGeest and associates[16] who demonstrated that vagal stimulation to the paced isovolumetric left ventricle of the dog caused a reduction of ventricular systolic pressure Such evidence should stimulate more quantitative investigations of the relationship between vagal stimulation and Frank Starling forces on ventricular function

The mean arterial blood pressure of a duck during a dive does not change significantly [3] The pulse pressure was always increased because of a decreased end diastolic pressure and sometimes a slightly increased peak systolic pressure.

The maintenance of the arterial blood pressure during the time that the cardiac output is decreasing indicates the peripheral resistance must be increasing Studies on the circulation through skeletal muscle showed that the flow was stopped during the period of the dive [4,17] Since a submerged animal is usually quite active the oxygen demands of the skeletal muscle will be increased If flow were only slowed and not stopped during the dive the uptake of oxygen would be increased and the stores of oxygen rapidly depleted The mechanism of energy supply to skeletal muscle contraction during a dive needs further experimental illumination

The web of the duck not only is an adaptation for a swimming mechanism but it also has peripheral A V anastomoses which must act as a temperature-regulating mechanism There was an intense sympathetic constriction when the duck was excited. However in the calm, habituated duck during a dive there was little change in the blood flow through the web.[11] The oxygen demand of the tissue of the web is low thereby eliminating the practical necessity for decreasing the blood flow during a dive. This circulation may play an important role in keeping the blood contained in the peripheral vasculature moving back to the heart allowing the essential tissues, the brain and heart, to most fully utilize the oxygen stored in the blood during the dive.

Within 1 to 2 seconds after emersion the reflex pattern is reversed[1] There is an intense tachycardia as a result of sympathetic stimulation and a removal of vagal inhibition. The reversal of autonomic response occurs so rapidly that not only does the cardiac output increase due to the increased heart rate but also due to the increased stroke volume resulting from the Frank Starling forces. Since the sympathetic peripheral vasoconstriction is not reversed as rapidly as the heart rate there is a significant increase in arterial blood pressure that gradually returns to the control predive values as the cardiac output and peripheral resistance return to the control values.

One important concept that emerged from this work was that the sympathetic control is not generalized but appears to be designed for highly differentiated action. During the dive there is decreased sympathetic activity to the heart and an increased sympathetic activity to the peripheral vessels. In the postdive period the sympathetic activity to the heart is rapidly enhanced and the sympathetic action on the peripheral blood vessels is decreased. The receptors and afferent pathways involved in this dramatic reversal of efferent discharge pattern are largely unknown. However experiments by Folkow and Rubenstein[9] suggest that pulmonary stretch receptors stimulated by restored respiration during the postdive period may be involved

Interference with any of the neurogenic links involved in the cardiovascular adjustments to diving will alter or abolish the characteristic response necessary to maintain blood flow to the essential organs, the heart and brain The elimination of the intense bradycardia by atropine or vagotomy prevents the peripheral vasoconstriction with the result that the animal will rapidly drown if kept submerged. Since there is still a slight bradycardia following atropine or vagotomy there must be a central inhibition of the sympathetic activity to the heart. Though beta blockade eliminates most of the tachycardia during the immediate postdive period central inhibition of vagal effect on the heart causes a small but clear increase in heart rate. The two nervous links to the heart seem to act in a reciprocal fashion in both the dive and postdive periods.

While a duck in a diving state adjusts to the anoxic environment by conserving the oxygen stores for the most important tissues for survival a duck in the alarmed state will usually attempt to escape by flying away The cardiovascular adjustments, in the form of the defence reaction which are required and known to be elicited in the alarmed state, are essentially opposite to those of the diving state.[4] This defence reaction is characterized by tachycardia an increased cardiac output, and a decreased peripheral resistance in the skeletal muscles, at least in the early phases of the reaction. The physiological balance of the autonomic control of the heart and blood vessels will naturally become affected in situations where these oppositely directed responses are simultaneously induced Frequently the ducks, when alarmed showed irregularities in their diving responses in the form of intermittent periods of tachycardia brief pressure rises, etc. suggesting an intermittent breakthrough of a competing defence reaction" The "calmer" and more relaxed the ducks were usually the more intense and regular was the diving response

The situation may however be very different in diving animals where alarm situations normally lead to diving as the natural way of escape. Here it may be expected that the autonomic adjustments typical of the diving reflex, rather than

those characterizing the above mentioned "defence reaction" are preferentially induced when such animals become alarmed. This view is supported by the observation that sudden sounds, threatening movements, etc. usually elicit a prompt bradycardia in seals[4] rather than the tachycardia typical of the "defence reaction" seen in ducks when similarly exposed. Therefore while an alarm situation in the duck tends to interfere with and suppress the diving reflex, it might reinforce the diving reflex in species like the seal.

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Clinical pharmacologic evaluation of the antiatherosclerotic agent, pyridinolcarbamate
A double-blind crossover trial in the treatment of atherosclerosis obliterans

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Toshiyuki Atsumi, M.D.
Sekiya Yamashita, M.D.
Takeshi Motomiya, M.D.
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Tadao Ishioka, M.D.
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Pyridinolcarbamate[1] has been shown to prevent the edematous arterial reaction and to induce definite regressive changes in the atheromatous lesions of rabbit arteries which show a relatively close resemblance to human arteries in their morphologic[4] and chemical aspects. Specifically, the edematous feature disappeared rapidly after administration of pyridinolcarbamate. In the course of 6 to 20 weeks of treatment, the atheromatous mass was definitely absorbed and replaced mainly by regenerated smooth muscle fibers as well as collagenous and elastic fibers. It is important to note that the compound is tolerated[7] by man in the full antiatherosclerotic dosages used experimentally on animals.

In human atherosclerosis, pathologic features similar to those found in animals have been clearly recognized. Even in patients with advanced atherosclerotic lesions, including organized and calcified lesions, there are still edematous and atheromatous parts which narrow the lumen of the artery and its branches and produce some local signs of the atherosclerotic disorder.

After the administration of pyridinolcarbamate there is an expansion of the arterial lumen in such edematous and atheromatous parts, and this is presumed to be induced by the drug. It is to be expected that such an improvement would be reflected in the relief of some local signs observed in atherosclerotic patients.

In order to assess the antiatherosclerotic effect of pyridinolcarbamate in man, controlled clinical trials have been performed on patients suffering from atherosclerotic diseases. For these trials atherosclerosis of arteries of the extremities has been found

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most appropriate for observation for in this morbid condition the ischemic signs in the end organs of affected arteries are directly visible making evaluation of treatment relatively easy

Any tests of drug effect in such a chronic disease should exclude the contamination of placebo effect and of spontaneous fluctuation of symptoms Also individual variations in response originating from differences in constitution social factors and stage of the disease should also be excluded insofar as this is possible

This paper describes a clinical trial with pyridinolcarbamate on 43 patients suffering from atherosclerosis obliterans with relatively stable signs. The results were obtained and evaluated by the double-blind crossover technique [8] To exclude the variables mentioned above a within subject comparison has been applied for the first time in a clinical trial of this nature

Materials and methods

The test subjects were male outpatients (age 33 to 79 years average 57 1 ± 13 9 years) suffering from atherosclerosis obliterans of a lower extremity with relatively stable signs and a claudication time of 5 minutes or less (average 1 min 41 sec ± 8 sec, with standard error) Diagnosis was made according to the criteria of McPherson and associates [9] based on clinical angiographic and plethysmographic [1 4] signs. Atherosclerosis obliterans, instead of arteriosclerosis obliterans was given as the diagnosis because in our department autopsy data has always revealed various stages of atherosclerotic changes in patients diagnosed as having arteriosclerosis obliterans. In 12 patients (13 legs) there was aortoiliac artery occlusion and the remaining 31 patients (48 legs) had femoral popliteal artery occlusion

The previous duration of individual signs of the affected limbs were as follows intermittent claudication (right leg 11 left leg 10 both legs 2?) 50 ± 56 5 months (1 to 240 months) local ischemic pain (right leg 3) 3 to 29 months paresthesia (right leg 2 left leg 3 both legs 1) 13 0 ± 3 8 months (1 to 29 months) local cyanosis (right leg 5 left leg 1) 18 to 26 months and ischemic ulcer (right leg 1) 3 months.

Two cases had a history of myocardial infarction and 5 cases had mild diabetes mellitus manifested by an abnormality in the glucose tolerance test but their fasting blood sugars remained within the normal range while receiving dietary treatment only Twenty-six cases had mild hypertension (essential) with average systolic blood pressure of 162 ± 34 6 and diastolic of 89 3 ± 38 1 one had a slight hypercholesterolemia (268 mg per 100 ml) The average serum cholesterol level (all cases) was 171 ± 36 7 mg per 100 ml

Planning A previous clinical trial of pyridinolcarbamate[4] was conducted on 126 patients (121 male and 5 female ages 23 to 72 years average 45 5 ± 13 0 years) suffering from atherosclerosis obliterans. Improvement started relatively early (within 10 weeks of treatment) in 24 of the 126 cases with impaired or absent arterial pulsation in 40 of the 95 cases with intermittent claudication in 9 of the 26 cases with gangrenous ulcer in 7 of the 18 cases with cyanosis in 18 of the 30 cases with pain and in 9 of the 27 cases with paresthesia respectively Thus the beginnings of improvement by these criteria were noted in 50 to 85 per cent of symptoms in 69 of all 126 patients within the first 10 weeks of treatment Based on such results the 10 week double-blind crossover trial was planned for the present investigation as detailed below

Details of crossover trial All patients were administered a placebo for the first 3 weeks as a wash-out period Needless to say the attending physicians and patients had no information about the medication They were thereafter divided into two groups by using random number tables The patients of one group received pyridinolcarbamate in a daily dose of 1 5 Gm (6 tablets) during the first 10 week period Two tablets were given with or directly after each meal The patients in the other group received a placebo of the same appearance size and flavor in exactly the same manner for the first 10 week period

Thereafter the first group of patients received placebo and the second group received pyridinolcarbamate for another 10 week period The attending physicians did not know of the planning and simply observed the clinical signs every week or two

in the outpatient department. For these patients hospitalization or treatment such as exercise or other drug therapy was strictly prohibited

After the end of the second 10 week period the changes in all clinical signs during each period were analyzed by the attending physicians and also by specialists from outside the study Intermittent claudication cyanosis, ischemic ulcer pain paresthesia and plethysmographic findings were the major signs to be evaluated

Attending physicians, Drs. Atsumi and Yamashita measured claudication time by stopwatch walking with the patients at the constant pace of 120 steps per minute in an air-conditioned corridor of the outpatient department. (The repeat variability of claudication time thus measured in the patients with a claudication time of less than 5 minutes in the previous group of 126 cases, was 24 4 $\pm$ 38.5 sec and it remained within 1 min in 89 5 per cent of all cases.)

Toe plethysmography[13, 14] was performed on the second toe before the trial and at the end of each 10 week period The crest time in second over cycle length in seconds $\left(\frac{CT}{CL}\right)$ was calculated to obtain the relative crest time because its reproducibility after repeated tests on the same person is marked as shown by Mune[15] Jungmann and Rohr[16] and by our own work (The mean crest time and the standard deviation measured in healthy persons in our outpatient department was 0 19 $\pm$ 0 18 and those measured in the previous group of patients suffering from atherosclerosis obliterans with the measurable crest time was 0.31 $\pm$ 0 13 The repeat variability of the relative crest time in these patients was small mounting to less than 0 07 sec and the relative crest time less than 0.07) These pneumoplethysmograms were recorded by Nihonkoden Multiplex Monitor Recorder (RM 150) The electric transducer used was the Statham unbounded strain-gauge transducer of DLPL -0 05 produced by Toyo Measure Industry Co Ltd The electrocardiogram (ECG) was recorded concomitantly and blood pressure was measured.

Routine clinical tests of the university hospital were performed in all cases, including blood analysis, urinalysis blood urea nitrogen serum cholesterol serum glutamic oxalacetic transaminase serum glutamic pyruvic transaminase, alkaline phosphatase bilirubin blood pressure eyeground photography chest x ray and ECG Inquiry concerning subjective symptoms was conducted according to a formula devised by psychologists in order to avoid the special attention of patients to individual symptoms.

A comparison of the effect of 10 weeks of treatment with pyridinolcarbamate and that of 10 weeks of treatment with placebo on each symptom was performed statistically at the end of trials. The dropout cases were also carefully analyzed This trial started in October 1967 just preceding the cold season of Tokyo and was completed in March 1968

Results

Twenty four patients finished the entire course of trials consisting of a 3 week reference (placebo-washout) period and the first and second 10 week regimens. Ten patients (10 legs) had aortoiliac artery occlusion and 14 patients (21 legs) had femoral popliteal artery occlusion

The preference for pyridinolcarbamate over placebo was established in the first, second third fourth sixth seventh eighth ninth tenth eleventh thirteenth fifteenth sixteenth seventeenth eighteenth nineteenth twenty-second and twenty third cases by the improvement in claudication time cyanosis, ulcer pain and paresthesia as shown in Tables I and II Thus the preference for pyridinolcarbamate had been statistically established ($p<0.01$)

Analysis of claudication time Twenty patients among 24 who completed the entire period of the double-blind crossover trial were subjected to analysis of claudication time. In 5 cases ulcer formation or other obstacles prohibited the measurement. The average claudication time measured immediately before the trial was 1 min. 41 sec $\pm$ 11 sec. and it was 2 min 18 sec. $\pm$ 1 sec at the third week i.e immediately before the first 10 week regimen There was a slight increase in claudication time during the 3 week placebo-wash-out period but it was statistically insignificant

Table I Treatment with pyridinolcarbamate and placebo in atherosclerosis obliterans—A double-blind crossover trial

Patient Nr	History	Arterial Pulsation	l	r	Symptoms	Placebo 0	1	3	1st Regimen 5	7	9	11	13	2nd Regimen 15	17	19	21	23 wks	Preference
No 1	7M	F	–	+	Claudicat on Ti e	49	1 04	1 26	1 15	1 29	2 08	2 13	1 56*	2 32	3 00	3 04	3 07	3 35	PYR
		P	±	+	Cya osis	–	–	–	–	–	–	±	±	±	±	–	–	–	
65yr M		DP	±	+	Pa n	–	–	–	–	–	–	–	–	–	–	–	–	–	
					P resthes a	–	–	–	–	–	–	–	–	–	–	–	–	–	
		TP	–	+	Plethysmogram(CT/CL) l	0 26						0 32(Δ+0 06)					0 24(Δ–0 08)		
					r	0,19						0,13(Δ–0,06)					0,12(Δ 0,01)		
No 2	2Y	F	+	+	Claudication Time	1 55	2 00	2 22'	2 43*	2 13	3 00	3 28	4 10	3 38	3 27*	3 08	5 30	4 30	PYR
		P	–	+	Cyanosis	–	–	–	–	–	–	–	–	±	–	–	–	+	
62yr M		DP	–	+	Pa	–	–	–	–	–	–	–	–	–	–	–	–	–	
					Pa esthesia	–	–	–	–	–	–	–	–	–	–	–	–	–	
		TP	–	–	Plethysmogram(CT/CL) l	0 41						0 32(Δ–0 09)*					0 38(Δ+0 06)		
					r	0 21						0,13(Δ 0,08)					0 15(Δ+0,02)		
No 3	2Y6M	F	–	+	Cl udicat on Time	28	51	55	1 32	1 02*	1 32	1 24	2 03	3 03	3 54	3 43	6 48	4 04*	PYR
		P	–	+	Cy nos s	+	+	+	+	+	+	+	+	+	+	+	+	+	
46yr M,		DP	–	+	P n	–	–	–	–	–	–	–	–	–	–	–	–	–	
					Paresthesia	+	+	+	+	+	+	+	+	+	+	+	+	+	
		TP	–	+	Plethysmogram(CT/CL) l								0 44				0 48(Δ+0 04)		
					r	0,13							0,17(Δ+0,04)				0 17(Δ0)		
No 4	1M	F	–	+	Claud cation Time	50	53	1 25*	1 24	1 25	1 48	1 58	2 10	2 27*	2 30	2 30	2 56	2 54	PYR
		P	–	–	Cyanosis	–	–	–	–	–	–	–	–	–	–	–	–	–	
40yr M		DP	–	+	Pain	–	–	–	–	–	–	–	–	–	–	–	–	–	
					Paresthesia	+	±	–	–	–	–	–	–	–	–	–	–	–	
		TP	–	+	Plethysmogram(CT/CL) l	0 29								0 26(Δ–0 03)			0 23(Δ–0 03)		
					r	0 24								0 21(Δ 0 03)			0 18(Δ 0 03)		
No 5	6M	F	+	–	Claudicat on Time	1 41	1 33	1 55	1 44	1 31	2 02	2 03	2 39	2 22*	3 05	2 34	2 30	2 50	no
		P	+	–	Cyanos s	–	–	–	–	–	–	–	–	–	–	–	–	–	
70yr M		DP	+	–	Pain	–	–	–	–	–	–	–	–	–	–	–	–	–	
					Paresthesia	–	–	–	–	–	–	–	–	–	–	–	–	–	
		TP	+	–	Plethysmogram(CT/CL) l	0 24							0 24 (Δ0)				0 28(Δ+0 04)		
					r	0,34							0 33(Δ 0,01)				0,32(Δ–0,01)		
No 6	5M	F	+	±	Claud cat on Time	1 03	2 03	2 46*	1 30*	2 30	2 18	2 45	2 22			2 14	2 13	1 45*	PYR
		P	+	–	Cy nosis	–	–	–	–	–	–	–	–			–	–	–	
61yr M		DP	+	–	Pain	–	–	–	–	–	–	–	–			–	–	–	
					Paresthesia	–	–	–	–	–	–	–	–			–	–	–	
		TP	+	–	Plethysmogram(CT/CL) l	0 16								0 26(Δ+0 10)*			0 18(Δ 0 08)		
					r	0,31								0 39(Δ+0,08)*			0,24(Δ–0,15)		
No 7	1Y5M	F	+	+	Claud cation Time	1 04	1 29	1 07*	1 20	1 52	1 45	1 50	2 22	2 18	1 52	2 05	2 15		PYR
		P	–	+	Cyanos s	–	–	–	–	–	–	–	–	–	–	–	–	–	
67yr M		DP	–	+	Pain	–	–	–	–	–	–	–	–	–	–	–	–	–	
					Paresthes a	–	–	–	+	+	+	+	+	–	–	–	–	–	
		TP	–	+	Plethysmogram(CT/CL) l	0 25							0 36(Δ+0 11)				0 28(Δ 0 08)		
						0,24							0 34(Δ+0 10)				0,25(Δ 0,09)		
No 8	2Y7M	F	+	+	Cl udication T me	1 34	2 21	2 31	3 10	3 20	4 30*	3 26	7 33	6 32	5 07	11 00	11 51	10 30*	PYR
		P	+	+	Cyanosis	–	–	–	–	–	–	–	–	–	–	–	–	–	
79yr M		DP	+	±	Pai	–	–	–	–	–	–	–	–	–	–	–	+*	+*	
					Paresthesia	–	–	–	–	–	–	–	–	–	–	–	–	–	
		TP	+	+	Plethys ogram(CT/CL) l	0 23						0 22(Δ 0 01)					0 19(Δ–0 05)		
						0,19						0 20(Δ 0 01)					0,17(Δ–0,05)		

Patient No. Age Sex	Duration	Art. pulsation (l r)	Symptoms	0	1	3	5	7	9	11	13	15	17	19	21	23 week	After
No. 9 67y M	9M	F ± ± P ± DP TP + ±	Claudication time Cyanosis Pain at rest Paresthesia Plethysmogram (CT/CL) l / r	3'45 0.20	3'14	5'00	4'25	4'58	4'37	5'27* 0.30(+0.10) 0.23	4'39	5'46	6'08	6'18*	7'30 0.24(–0.06) 0.19(–0.01)	6'45	PYR
No. 10 41y M	18Y	F + + P + DP + – TP –	Claudication time Cyanosis Pain Paresthesia Plethysmogram (CT/CL) l / r	2'08 0.28	1'24	51	17	1'01	2'16	55 0.33(–0.05)	1'26*	Ulc	1		alk 0.24(–0.09)	9	PYR
No. 11 62y M	20Y	F + P – DP – – TP	Claudication time Cyanosis Pain Pain at rest Plethysmogram (CT/CL) l / r	1'24 0.38 0.24	1'07*	1'59*	2'00*	4'51*	5'52*	6'15* 0.30(–0.07) 0.20(–0.01)	6'12	4'13*	4'52*	5'12*			PYR
No. 12 77y M	3Y	F + P – DP – TP –	Claudication time Cyanosis Pain Paresthesia Plethysmogram (CT/CL) l / r	1'35*	2'10*	2'06*	2'14*	2'43*	2'09	2'35		1'45*		1'49*		2'28	PP
No. 13 64y M	5Y	F + + P DP – TP – –	Claudication time Cyanosis Pain Paresthesia Plethysmogram (CT/CL) l / r	1'37* 0.36 0.37	1'40	2'27	2'57*	3'02*	3'29*	4'14* 0.38(+0.02) 0.32(–0.05)	4'15*	4'42	2'52	3'13	2'45	2'46	PYR
No. 14 51y M	6Y	F – + P + DP – – TP – –	Claudication time Cyanosis Pain at rest Plethysmogram (CT/CL) l / r	1'04	2'10	3'01*	5'11	3'21	3'58*	3'20	4'35*	3'57	4'03*	5'17	4'18 0.46	5'32	
No. 15 45y M	12 13Y	F + + P + + DP + – TP + +	Claudication time Cyanosis Pain Paresthesia Plethysmogram (CT/CL) l / r	1'51* 0.11 0.30	1'52*	1'59*	3'31*	3'14		3'30* 0.14(+0.03) 0.23(–0.07)*	5'45*	5'17*	2'55*	6'03	5'08* 0.14(+0.0) 0.26(+0.03)	4'46	PYR
No. 16 60y M	2Y	F ± + P – + DP – + TP – +	Claudication time Cyanosis Pain Paresthesia Plethysmogram (CT/CL) l / r	1'29* 0.24	1'57*	1'52*	2'15	2'07	2'53	2'40 0.17(+0.07)*		2'48	2'34	2'32 0.51 0.13(–0.04)	2'21*		PYR

The claudication time was measured by the walking rate of 120 steps per minute.
F: A. femoralis; P: A. poplitea; DP: A. dorsalis pedis; TP: A. tibialis posterior.
CT/CL: crest time (second) per cycle length in seconds.
▲: the difference from the foregoing CT/CL value.
significant improvement (*) or aggravating ( ).

Hatched: Pyridinolcarbamate Treatment
Blank: Placebo Treatment

Continued on following page.

Table I—cont d

Patient Nr	History	Arterial Pulsation	l	r	Symptoms	Placebo 0	1	3	1st Regimen 5	7	9	11	13	2nd Regimen 15	17	19	21	23 weeks	Preference
No 17 51yr M	6M	F	+	+	Claud cat on Ti e	3'03"	2'50"	3 27	4 06	4 33	4 27		3 00	3 42	2'58"	3 46	4'27		PYR
		P	−	−	Cyanosis	−	−	−	−	−	−		−	−	−	−	−		
		DP	−	+	Pain	−	−	−	−	−	−		−	−	−	−	−		
		TP	−	−	Paresthes a	−	−	−	−	−	−		−	−	−	−	−		
					Plethysmogr m(CT/CL) l	0 18						0 29(Δ+0 11)					0 21(Δ 0 08)		
					r	0,20						0,22(Δ 0,02)					0,20(Δ−0,02)		
No 18 42yr M	3M	F	+	+	Ulcer	+	+	+	−	−	−	−	−	−	−	−	−	−	PYR
		P	+	−	Cyanosis	+	+	+	*	*	−	+	+	−	−	−	−	−	
		DP	+	−	P n	+	+	+	−	−	−	−	−	−	−	−	−	−	
		TP	+	−	Paresthesia	−	−	−	−	−	−	−	−	−	−	−	−	−	
					Plethys ogr m(CT/CL) l	0 27						0 13(Δ−0 14)					0 12(Δ−0 01)		
					r	0,41						0,37(Δ 0 04)							
No 19 49yr M	1M	F	+	+	Claudicat on Time	1'01	1 30"	1'55	2 00		2 27		3 09	2 50	3 06	2'09"	2 25	2 45	PYR
		P	+	+	Cya osis	−	−	−	−		−		−	−	−	−	−	−	
		DP	+	+	Pa n	−	−	−	−		−		−	−	−	−	−	−	
		TP	+	−	Paresthes	−	−	−	−		−		−	−	−	−	−	−	
					Plethysmogr m(CT/CL) l	0 23						0 17(Δ 0 06)							
					r	0,24						0,15(Δ 0,09)							
No 20 71yr M	1Y1M	F	−	+	Cl ud cat on T me		1 57	2 19"	2 31	2'28	2 33	2 28	2 28"	2 45	2'53"	2 45	2'28"		no
		P	−	−	Cyanos s	−	−	−	−	−	−	−	−	−	−	−	−		
		DP	−	+	Pa	−	−	−	−	−	−	−	−	−	−	−	−		
		TP	−	−	Paresthes a	−	−	−	−	−	−	−	−	−	−	−	−		
					Plethysmogram(CT/CL) l	0 48						0 25(Δ0)					0,20(Δ−0,05)		
					r	0,25													
No 21 35yr M	1Y4M	F	+	+	Claud o t on Time	4 20	3 44		3 34	5 27		5 55		5 03	5 40	4 20	5 33	6 05	no
		P	+	+	Cyanosis	−	−		−	−		−		−	−	−	−	−	
		DP	−	+	Pa n	−	−		−	−		−		−	−	−	−	−	
		TP	−	+	P r sthes a	−	−		−	−		−		−	−	−	−	−	
					Plethysmog a (CT/CL) l	0 26							0 24(Δ−0 02)				0 22(Δ 0 02)		
					r	0,15							0,18(Δ 0,03)				0,13(Δ−0,05)		
No 22 40yr M	1Y3M	F	+	+	Claudicat on T me	2 48		2 24	3'01	2'30"	2'56"	3 18	2 54"	Ulcer limited the alking					PYR
		P	+	−	Ulc	−		−	−	−	−	−	−	+	+	−	−	−	
		DP	−	−	Cy nosis	*	*	+	+	+	+	■	■	■	⊥	■	−	+	
		TP	−	−	Pa	−	−	−	−	−	−	−	−	−	−	−	−	−	
					Pa esthes a	−	−	−	−	−	−	−	−	−	−	−	−	−	
					Plethysmogr m(CT/CL) l	0 45						0 44(Δ 0 01)				0,44			
					r														
No 23 33yr M	1Y	F	+	+	Claud cat o T me	2 40	46	3 04"	2 20	3 04	3'22"		4 01		3 24		4 17	56	PYR
		P	+	+	Ulce	+	+	+	+	+	+	−	−		−	+	−	−	
		DP	−	−	Cy nos s	*	+	−	−	+	+	+	+		+	+	+	+	
		TP	+	−	Parm	−	−	−	−	−	−	−	−		−	+	−	−	
					Pareath a a	−	−	+	−	−	−	−	−		−	−	−	−	
					Plethysmog am(CT/CL) l														
No 24 56yr M	4M	F	+	+	Cla d cat on T me	2'40"	2 07	2'24"			2 26	5 21		3 32"	4 25	3 49	3 17	5 45	•
		P	+	−	Cyanos a	−	−	−			−	−		−	−	−	−	−	
		TP	+	−	P	−	−	−			−	−		−	−	−	−	−	
		DP	+	−	Paresthes a	−	−	−			−	−		−	−	−	−	−	
					Plethysmogram(CT/CL) l	0 28									0 27(Δ−0 01)				
					r	0 40									0,37(Δ−0 03)				

The claud cat on t me as measu ed by the walk ng rat of 120 t p per ute
F A temo l a P A popl t DP A de a l a p d a TP A tib l p t
CT/CL are t t a a d pe yel l gth l d
▲ th diff from the t g a CT/CL l
la l l lmp me ( ) ver ( )

[shaded box] Py d l h mat T tme t

[blank box] Pl b T tme

In each patient two regression lines of claudication time based upon each 10 weeks of treatment are compared with the data of pyridinolcarbamate and placebo periods respectively. The calculation is in general, carried out on the basis of the data obtained biweekly during each treatment of 10 weeks. In Table II are given patient no. sequence of treatment, regression coefficients for pyridinolcarbamate and placebo periods, difference in regression coefficients, and initial claudication time at the third week of the preceding period of placebo wash out.

Of all 20 cases listed in Table II 16 show positive values for the difference in regression coefficients that is, the average effect of pyridinolcarbamate on the prolongation of claudication time exceeds that of the placebo in 80 per cent of the cases (with 95 per cent confidence limits of 56.3 and 94 3 per cent)

Assuming that the differences in regression coefficients distribute normally one may evaluate quantitatively the effect of pyridinolcarbamate upon the prolongation of claudication time. The mean value of the difference in regression coefficients between pyridinolcarbamate and placebo regimens is estimated to be 7 03 sec. per week (with 95 per cent confidence limits of 2 21 and 11.85 sec. per week) on the basis of the data, in which the eleventh case has been eliminated as an outlier by Smirnoff's test. There is no apparent correlation between the difference in regression coefficients and the initial claudication time.

In conclusion the claudication time in the present type of patient has been shown to be prolonged more by pyridinolcarbamate than by placebo in 80 per cent of the cases and the difference in prolongation has been estimated to be 7 03 sec. weekly on the average

In claudication times measured during treatment a steady increase of more than

Table II

Patient No.	Sequence of treatment	Regression coefficient (sec./week)		Difference per week (sec./week)	CL-T ime (sec.) (3rd week)
		PY	P		
1	P PY	6 65	6 30	0 35	86
2	PY P	12 45	11 35	1 10	142
3	P PY	9 10	4 20	4 90	55
4	PY P	6 44	4 13	2 31	85
5	PY P	7 10	−1 52	8 62	115
6	P PY	−6 08	5 95	−12 03	166
7	P PY	0 20	6 10	−5 9	67
8	P PY	49 00	26 90	22 10	151
9	P PY	8 95	3 39	5 56	300
11	PY P	24 79	−30 25	55 04	119
12	P PY	7 67	1 45	6 22	126
13	PY P	11 40	−9 51	20 91	147
14	P PY	9 11	−3 65	12 76	181
15	PY P	14 10	1 56	12 54	119
16	PY P	2 96	−1 92	4 88	112
17	P PY	6 89	−9 34	16 23	207
19	PY P	6 57	−1 43	8 00	115
20	P PY	−2 95	−0 30	−2 65	139
21	PY P	7 09	7 40	−0 31	224
23	PY P	15 50	−12 49	27 99	184
N = 19	M	4 06	2 03	7 03	143 2

P: Placebo
PY: pyridinolcarbamate
*Patient No. 11 was eliminated by Smirnoff method.

Table III Effect of pyridinolcarbamate and placebo treatment in 24 patients who finished the whole regimen (and those in all 43 patients including dropout cases shown in parentheses)

Parameters	No. measured or observed	Pyridinolcarbamate	Placebo
Claudication time	No. measured	21 (32)	23 (30)
No. prolonged	over 1 minute	11 (17)	6 (8)
No. shortened	over 1 minute	0 (0)	3 (3)
Crest time $\left(\frac{CT}{CL}\right)$	No. measured	21 (22)	18 (19)
No. shortened	over 0.07	11† (12†)	0 (0)
No. prolonged	over 0.07	0 (0)	4 (5)
Impaired pulsation	No. observed	23 (29)	17 (18)
No. reappeared		‡ (10‡)	0 (0)
No. disappeared		0 (0)	0 (1)
Cyanosis	No. observed	7 (8)	7 (9)
No. disappeared		3 (3)	0 (0)
No. appeared		0 (0)	3 (4)
Ischemic pain	No. observed	2 (4)	2 (3)
No. disappeared		1 (2)	0 (0)
No. appeared		0 (0)	1 (2)
Paresthesia	No. observed	4 (6)	4 (5)
No. disappeared		2 (0)	0 (0)
No. appeared		0 (0)	2 (3)
Ischemic ulcer	No. observed	3 (3)	3 (3)
No. healed		3 (3)	0 (0)
No. appeared		0 (0)	2 (3)

The parenthesized number re the sum of all patient ncluding dropout cases
*See Table II.
†p <0.01
‡p <0.05.

1 min (120 steps) was observed in 11 cases in the course of 2 to 8 weeks (average 6) on pyridinolcarbamate and in 6 cases in 6 to 10 weeks (average 9) on placebo as shown in Tables I and III The prolongation of claudication time over 2 minutes was encountered in 6 cases in the course of 8 to 10 weeks on pyridinolcarbamate and in one case on placebo at the end of 10 weeks. In 9 cases exhibiting an increase in claudication time of more than 1 min a 10 week period on pyridinolcarbamate was followed by a like period on placebo However in all of these cases except 3 claudication time continued to lengthen slowly during the following 10 weeks on placebo although not so much as in the cases on the drug In the thirteenth case claudication time was reduced by 1 min at the end of the fourth week on placebo subsequently the patient began to suffer from paresthesia of the left foot at the end of 6 weeks and this continued through the tenth week

The preference for pyridinolcarbamate over placebo was also established independently and statistically significantly by the definite reduction of crest time (i e over 0 07 sec and $\frac{CT}{CL}$ over 0 07) alone as seen in the first second sixth seventh tenth eleventh fifteenth sixteenth seventeenth eighteenth and nineteenth patients as shown in Table I and Figs 1 and 2 There was also a good correlation between the prolongation of claudication and the shortening in relative crest time ($p < 0.05$) as shown in Fig 3

The crest time lengthened after 10 weeks on placebo in the sixth seventh ninth and seventeenth cases however no case exhibited a prolongation after the pyridinolcarbamate period As a consequence the preference for pyridinolcarbamate over placebo was established in 18 cases out of the 24 exceptions being the fifth twelfth twentieth twenty first and twenty fourth cases in which no preference was determined No case exhibited a preference

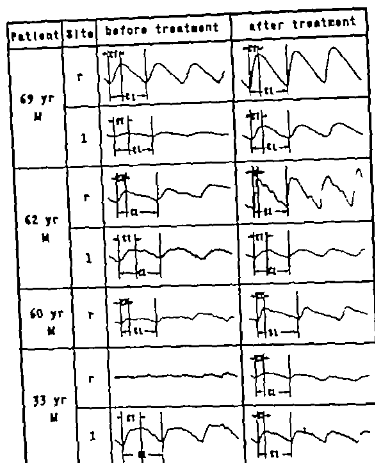


Fig. 1. Improvement in digital plethysmogram after 10 weeks treatment with pyridinolcarbamate in arteriosclerosis obliterans.

for placebo either in the evaluation of the above mentioned five major clinical signs or in the plethysmographic sign alone.

The absent arterial pulsation reappeared in the left dorsal pedal artery of the first patient, in the femoral artery of the second patient, in the left femoral, popliteal, and dorsal pedal arteries of the eleventh patient, in the left femoral artery of the fourteenth patient, in the right dorsal pedal artery of the fifteenth patient, in the right popliteal artery of the eighteenth case, and in the left dorsal pedal artery of the twenty-first and twenty-second patients in the course of 10 weeks of pyridinolcarbamate treatment. In contrast, none showed improvement of impaired pulsation during placebo treatment.

Cyanosis disappeared in 3 of the 7 patients at the end of 2, 6, and 12 weeks, respectively, on pyridinolcarbamate and appeared or increased in 3 patients on placebo. In none of the 7 cyanosis cases on placebo did the symptom disappear. Pain disappeared in one of the 2 patients after 2 weeks on pyridinolcarbamate, but in neither of the 2 patients on placebo, and appeared in 1 on placebo. Paresthesia also disappeared in 2 of the 4 patients at the end of 2 and 8 weeks, respectively, on pyridinolcarbamate. On the other hand, paresthesia appeared in 2 patients on placebo after 2 and 8 weeks, respectively. None of the 4 paresthesia cases showed disappearance of symptoms during the placebo period. Ulcer healed in 3 patients at the end of 2, 6, and 8 weeks, respectively, on pyridinolcarbamate but in neither of 2 during the placebo period. Ulcer appeared in 2 patients on

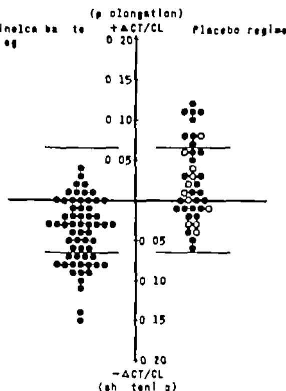


Fig 2 Difference of crest time (ΔCT/CL) in the digital plethysmogram which was measured before and after pyridinolcarbamate (10 weeks) or placebo (10 weeks) regimen in 38 patients.

placebo and was cured during the following pyridinolcarbamate period

As shown in Table IV transient gastric distress was encountered in 6 of the 24 patients during the pyridinolcarbamate period and also in 3 patients on placebo Diarrhea was encountered in 1 during the pyridinolcarbamate period An erythema type rash was encountered in 1 patient and dyspnea and palpitation in 1 patient during the placebo period

No significant abnormality other than the symptoms described was observed in the clinical or laboratory findings during either period of the trial

Dropout cases The reasons for dropping out show no significant difference between pyridinolcarbamate and placebo regimen

1 Five patients (men aged 69 62 64 68 and 53 years with histories of intermittent claudication lasting 5 3 10 3 and 2 years, respectively) received the preliminary 3 week placebo regimen and the 10 week pyridinolcarbamate treatment. During the following placebo period they withdrew from the trial at the end of 2 4 2 2 and 6 weeks respectively Their reasons were bronchial pneumonia (?) cystitis (1) change of residence (1) and unknown (1) One of these revisited the hospital and has been on pyridinolcarbamate ever since.

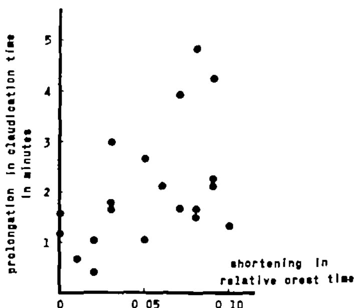


Fig 3 Correlation between improvement in claudication time (prolongation) and crest time (shortening) after 10 weeks of pyridinolcarbamate regimen The coefficient of the correlation is 0.47 and the correlation is statistically significant ($p < 0.05$).

Table IV Incidence of untoward effects encountered during pyridinolcarbamate or placebo period in 24 patients who finished the whole regimen (and those in all 43 patients including dropout cases shown in parentheses)

Side facts	Pyridinol-carbamate		Placebo	
Gastric distress	6	(7)	3	(5)
Diarrhea	1	(1)	0	(1)
Rash	0	(0)	1	(1)
Palpitation and dyspnea	0	(0)	1	(1)
P tient treated	24	(38)	24	(37)
Patients ith side effects	7	(8)	5	(8)

The parenthesized numbers are the sum of all patients including dropout cases.

During 10 weeks on pyridinolcarbamate 3 of the 5 patients concerned showed prolongation of claudication time and in 1 patient it was over 3 min In all three patients improvement started at the end of 4 weeks on pyridinolcarbamate. In one patient pain in the affected left foot disappeared at the end of 4 weeks on pyridinol carbamate. In one case the absent arterial pulsation reappeared n the right and left posterior tibial arteries and left popliteal artery at the end of the pyridinolcarbamate period concurrently crest time in the left second toe was reduced sign ficantly In another case pulsation reappeared in the left popliteal artery during pyridinol carbamate treatment In no patient did pulsation reappear on placebo.

Gastric distress was encountered in one case during the placebo period

2 Three patients (male, aged 62 77 and 78 years with histories of intermittent la dication lasting 10 years 1 year and 7 months, respectively) received the preliminary 3 weeks of placebo treatment and the follow ng 10 weeks of placebo. During the following pyrid nolcarbamate period they withdrew t the end of 6, 8 and 6 weeks, respectively The reasons in the first patient were his satisfaction with th treatment and n economic one Improvement of cl nical symptoms started at the end of two weeks on pyridinolcarbamate claudication time increased markedly cyanosis disappeared almost completely and the absent arterial pulsation reappeared in his right posterior tibial and dorsal pedal arteries within 6 weeks of treatment. The second patient exhibited a prolongation of crest time in the left second toe at the end of 10 weeks on placebo however there was a marked increase in claudication time during the following pyridinolcarbamate period He experienced gastric distress but his condition seemed to be satisfactory The third case suffered an accidental burn.

3 Six patients (men 36 35 50 59 70 and 47 years old) had histories of inter mittent claudication during the previous 8 years 5 years 2 years 9 months, 5 years, and 6 years, respectively After 3 weeks of placebo treatment they re ceived pyridinolcarbamate for 4 4 2 10 8 and 10 weeks respectively but withdrew The reasons were an operation for suspected gastric cancer (1) economic reasons (2) and presumable disappoint ment (3) Three patients received the drug over a period of 4 weeks and two of them exhibited marked lengthen ng of claudica tion time i.e. 1 min 11 sec and 3 min respectively

4 Five patients (men 74 35 66 64 and 37 years old) had histories of intermittent claudication lasting 6 13 2 5 and 3 years, respectively They underwent 3 weeks of preliminary placebo regimen and during the following placebo period they withdrew No case exhibited any noticeable improvement. One suffered from anorexia and gastric distress and finally had an attack of angina pectoris.

The effect of pyridinolcarbamate and placebo treatment in all 43 patients, includ ing dropout cases, has been summarized n Table III The claudication time was prolonged over one minute in 17 patients after drug regimen and in 8 patients after placebo regimen.

As shown in Figs. 1 and 2 crest time and relative crest time were measured before and after 10 weeks of drug or placebo ther py in 38 of all 43 patients. After th drug period crest time and relative crest time were shortened in 45 of all 60 legs they were over 0 07 sec and 0 07 respectively in 18 legs. After the placebo period they were also shortened slightly in 13 of all

39 legs however in no patient did the values exceed 0 07 sec Crest time and relative crest time were prolonged slightly less than 0 04 sec and 0 04 sec respectively in 8 legs after pyridinolcarbamate while they were prolonged in 22 cases after the placebo period There was no case exhibiting a prolongation of more than 0 07 sec after the drug period while 9 cases exhibited definite prolongation over 0 07 sec. after placebo In 11 legs of 7 patients who had received the foregoing drug regimen a further reduction of crest time was observed in 4 legs but none exceeds 0 07 sec while a slight prolongation was observed in 5 legs and it was over 0 07 sec in one case

As shown in Fig 3 claudication time and relative crest time were measured at the same time in 20 of all 43 cases before and after 10 weeks of pyridinolcarbamate therapy The coefficient of the correlation between prolongation of claudication time and shortening of relative crest time is 0 47 and thus is statistically significant at ($p < 0.05$)

Impaired arterial pulsation reappeared or improved markedly in 10 cases after the drug regimen and in none after the placebo regimen Cyanosis ulcer pain and paresthesia improved after drug therapy and in none after placebo while cyanosis pain paresthesia, and ischemic ulcer appeared in 2 3 and 4 patients respectively on placebo

The side effects encountered in all 43 patients are shown in Table IV The statistically significant therapeutic effect of pyridinolcarbamate without serious side effect has been clearly shown in these tables.

Discussion

The most important finding in this clinical pharmacological trial utilizing a double blind crossover technique was a statistically significant preference for pyridinolcarbamate over placebo. This was also confirmed by such objective signs as the shortening of crest time in plethysmographic observations. Such observations have never been reported previously in the drug therapy of atherosclerosis obliterans In the 24 cases suffering from atherosclerosis obliterans none showed preference for placebo over pyridinolcarbamate and even in the remaining dropout cases significant improvement was observed in each of the clinical signs during pyridinolcarbamate treatment

The effect of the compound was observed at the end of 4 to 6 weeks in the majority of cases. Improvement continued week after week not only in claudication time but also in the other symptoms such as cyanosis ulcer pain and paresthesia. After withdrawal of pyridinolcarbamate deterioration in some symptoms was found in 4 patients 2 showed a worsening of claudication time and paresthesia in the fourth and sixth week after withdrawal 2 patients exhibited a prolongation of crest time in plethysmography 10 weeks after drug withdrawal The remaining 5 patients showed no relapse and the beneficial effect continued for the following 10 weeks on placebo These facts demonstrate the slow acting and persisting effects of the compound

The compound has no vasodilative effect in therapeutic dosages and such an effect is unlikely to be encountered in clinical application Vasodilators prolong crest time and do not lead to the reduction of crest time commonly observed during pyridinolcarbamate treatment Actually the shortening of crest time in digital plethysmography which occurred in 11 cases after pyridinolcarbamate treatment, demonstrated the effect of the compound Reduction of crest time was not seen during or after the placebo period and in 4 cases the crest time was even prolonged after 13 weeks of placebo administration

The crest time has been shown to be practically independent of the heart rate pulse pressure stroke volume mean blood pressure and peripheral resistance by Simonson and associates[8] and Jungmann and Rohr[15,16] Dillon and Hertzman[17] also found the crest time on the fingers to be unaffected by alterations in vasotonus induced by cooling the contralateral hand Nor did sympathectomy cause any definite changes in the crest time[17] The reproducibility of repeated tests on the same person is marked and the crest time is highly constant in each individual person as mentioned above. Crest time[13] is said to decrease not only from expansion of the arterial lumen but also from a strong in-

crease in the cardiac stroke volume and a reduction in the viscosity of the blood.[19] However no direct cardiotonic effect from the use of pyridinolcarbamate was observed and also no change was found in blood pressure in the present test subjects. Reduction in blood viscosity is thought to be affected by reducing the content of hemoglobin, fibrinogen and possibly of cholesterol triglyceride, plasma protein and free fatty acids in the blood.[19] With the exception of fibrinogen no significant change in the proportion of these substances in the blood attributable to pyridinolcarbamate treatment has ever been observed. In some cases an elevated fibrinogen level was actually reduced and normalized during pyridinolcarbamate treatment.[1] However the beneficial effect of the compound was observed commonly without any appreciable change in fibrinogen content. Angiography often showed the unmistakable expansion of narrowed arterial segments and reopening of the branches from such segments at the same time the reappearance of absent arterial pulsation was observed as reported previously.[1,20,21]

Recently pyridinolcarbamate has been shown by us to definitely enhance the enzymatic activity of glycolytic enzymes, especially of glucose-6-phosphate dehydrogenase in the arterial wall and atheromatous lesions of rabbits and chicks and also to enhance the activity of ATPase and nucleotidase in their atheromatous lesions. It has also been shown by Lykke Willoughby and Koache[22] that pyridinolcarbamate antagonizes the vascular permeability-increasing effect of bradykinin RNA thymic permeability factor and lymph node permeability factor in mice and guinea pig while the lymph-node permeability factor has been known to stimulate an extensive emigration of leukocytes and the deposition of a material resembling connective-tissue fibrinoid. Moreover pyridinolcarbamate has been shown by Matsumoto and Sato[23] to prevent fibrinoid degeneration in small arteries and arterioles of Goldblatt's hypertensive rabbits and it has been shown also by Yoshida and associates[24] that the compound enhances the removal of fibrinoid substance deposited in the arterial walls of small arteries and arterioles of Goldblatt's hypertensive rats. The inhibitory activity of pyridinolcarbamate on the active and passive Arthus phenomenon in rabbits was found by Hashimoto and associates.[25] The antithrombotic effect of pyridinolcarbamate has also been demonstrated experimentally by Tsuchiya and co-workers[26] utilizing microcirculatory observations. Following the method of Veiner and Caen[27] pyridinolcarbamate, in a daily dose of 1.5 Gm given orally in man has been shown by us to reduce the ADP-induced platelet aggregation. The compound was originally made as a new type of agent capable of inhibiting the acute vascular changes induced by chemical (cholesterol etc.) and mechanical stresses. Spector and Willoughby[28] also noted its inhibitory activity on the acute vascular changes following experimental injury in their animals.

Such evidence suggests either a direct or indirect effect of pyridinolcarbamate on atherosclerotic changes in the edematous or atheromatous parts of affected arteries as in the case of atheromatous rabbits.

The slow-starting beneficial effect of the compound has been observed in a large number of patients suffering from atherosclerosis of the extremities and also in cerebral and coronary atherosclerosis.[1,4,20,21,29-31] Among 449 patients[29] suffering from moderate or severe arteriosclerosis obliterans who visited the university hospitals of Japan during the past 2 years and received pyridinolcarbamate treatment (1 to 1.5 Gm daily) 340 cases (77 per cent) were reported to be markedly improved by pyridinolcarbamate treatment without surgical procedures. It has been stated by many investigators[1,30] that in cases of angina pectoris and other symptoms of this disease the relapse rate after withdrawal of pyridinolcarbamate has been definitely reduced by previous long term (over 20 to 30 weeks) therapy with the compound. Such facts suggest an antiatherosclerotic effect of the compound in man however further histologic analysis is obviously needed.

Summary

The antiatherosclerotic effect of pyridinolcarbamate in man has been subjected to the present controlled clinical

trial in 43 patients suffering from atherosclerosis obliterans with relatively stable signs and short claudication times (101 ± 8 sec)

To isolate individual factors such as age sex constitution social condition and spontaneous fluctuations of symptoms from the drug effect a double blind crossover technique (within-subject comparison) has been applied After the initial 3 weeks of placebo wash out a 10 week regimen of placebo or pyridinolcarbamate (1 5 Gm daily) and another 10 weeks of alternative regimens were given successively

After drug regimen the prolonged crest time in plethysmography was shortened ($p < 0.01$) and claudication time prolonged with a statistically significant correlation ($p < 0.05$) The statistically significant preference for pyridinolcarbamate over placebo has been established by the effect on crest time alone claudication time alone and also major symptoms including ischemic ulcer cyanosis pain and paresthesia of affected legs ($p < 0.001$)

The relatively slow acting and persistent effect of pyridinolcarbamate on the clinical signs observed in these patients encourages further histologic analysis of its effect on atheromatous lesions in man

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posed by mitral stenosis on the cardiac output and demonstrated that this restriction fails to affect coronary blood flow and myocardial oxygen consumption which were normal both at rest and during exercise.[13] In that study it was demonstrated that the primary determinant of myocardial oxygen consumption in mitral stenosis was the PTM It was also found that heart rates inappropriately high for a given state result in energy expenditures above those required for maintenance of pressure and cardiac output. Like mitral stenosis, congenital heart lesions provide unique experiments of nature These lesions offer the opportunity to study the effects of chronic volume and pressure overload on left ventricular performance, coronary blood flow and myocardial oxygen usage *in young adults without myocardial disease who have never been in congestive heart failure and should be free of coronary disease*

Materials and methods

Nine patients with congenital heart lesions overloading the left ventricle (4 with patent ductus arteriosus, 2 with ventricular septal defect, and 3 with coarctation of the aorta) were studied These patients were selected from the considerably larger group of patients with congenital heart disease studied by us between 1963 and 1968 Selection was on the basis of the following criteria the patients were 13 years of age or older but less than 40 years of age in normal sinus rhythm and Class I A by Heart Association criteria had not required or received cardiac medication gave enlightened consent to the investigation and had satisfactory measurements of all variables studied including replicate measurements of variables relevant to the presence of physiological steady state. It must be emphasized that this sample was not intended to be representative of the pathophysiology of the congenital heart lesions but to provide a suitable group for study of the influence of pressure and volume overloading on left ventricular hemodynamics and metabolism. The stringency of the selection criteria restricted the number of patients and imposed limitations on conclusions permissible from statistical analyses of subgroups but assured that the significant observations on left ventricular energetics were made in compensated ventricles, without concomitant inflammatory degenerative or ischemic lesions.

Patients were studied in the fasting state following mild barbiturate sedation which was adjusted according to body weight. The pulmonary artery was catheterized through the right antecubital vein. The coronary sinus was entered through a left antecubital vein Care was taken to place the catheter high in the coronary sinus to avoid right atrial venous admixture. The left ventricle and aortic root were catheterized in a retrograde fashion through percutaneous puncture or arteriotomy of brachial or femoral arteries. Steady-state measurements of coronary blood flow cardiac output, and systemic and pulmonary arterial pressures were made at rest and during supine exercise on a bicycle ergometer

Pressures were measured using Statham P23Gb strain gauges and an Electronics for Medicine recorder calibrated directly with a mercury manometer The reference level for zero pressure was halfway from the manubrium to the table top Pressures were measured before, during and after each measurement of coronary blood flow in order to ascertain the presence of a steady state in all patients the three values for pressure and heart rate differed by less than 10 per cent both at rest and during exercise. Coronary blood flow (CBF) was measured by the nitrous oxide desaturation technique,[4] with use of a partition coefficient of 1 1 between blood and myocardium. Blood gases were analyzed by the technique of Van Slyke and Neill [4] Myocardial saturation was evidenced by arterial-coronary sinus nitrous oxide differences of less than 0.3 volumes per cent. In addition to pressure and heart rate data, evidence for a steady state during coronary blood flow measurement was provided by a good French-curve fit for all points on a linear plot of the nitrous oxide washout. Expired air and its oxygen content were measured as previously described.[13] Total left ventricular blood flow the volume of which is equal to pulmonary blood flow in all of these patients, was obtained as the quotient of the total body oxygen consumption and the pulmonary arterial aortic oxygen difference and systemic blood flow as the quotient of total

Left ventricular coronary flow, metabolism, and performance in mild congenital heart disease with increased left ventricular flow or pressure*

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Since the early part of this century investigations have been carried out in animals to demonstrate the relative importance of the various components of cardiac effort in determining myocardial oxygen consumption [1] The effects of heart rate [2,3] arterial pressure [4,7] cardiac output [4,8] velocity of ventricular contraction [9,10] and tension (or pressure) time index [11,12] as hemodynamic determinants of coronary blood flow and myocardial oxygen consumption have received particular attention In both the isolated supported heart[11] and the intact dog [13] the area under the left ventricular pressure curve the pressure time index (PTM) which Wiggers and Katz[14] suggested might be a better index of mechanical activity than useful external work performed appeared to be the primary determinant of myocardial oxygen requirements under the conditions of these experiments. However information obtained during the study of acute dog preparations altered by anesthesia and surgery is not necessarily applicable to human cardiac function either in patients with normal hearts or in chronic disease states Therefore it is important to determine the influence of chronic alterations in hemodynamics on myocardial oxygen requirements in man We have previously reported on the restriction im

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Table I. Coronary and systemic hemodynamics in patients with congenital heart disease

Subject (yr., sex, BSA)	Diagnosis	CBF	MVO	C(A-V)O₂ vol	$\dot{Q}F$	$\dot{Q}T$	Heart rate	Pressure (mm. Hg) Mean arterial	Pressure (mm. Hg) LVed	PTM	Stroke work index	MSER	TPR	CRI
1 16, F 1.27	PDA	118	14.1	12.0	3.44	4.61	105	102	5	2853	61.0	228	1765	0.86
		145†	17.6	12.1	—	5.16	144	101	1	3068	51.4	237	—	0.70
2 30, F 1.40	PDA	97	10.2	10.5	3.22	3.86	75	100	11	3067	81.8	227	1778	1.03
		141	13.3	10.0	—	3.86	136	110	12	4094	64.7	251	—	0.78
3 13, M 1.39	PDA	101	13.3	13.1	4.12	7.05	116	93	10	3205	89.6	361	1299	0.92
		122	16.0	13.2	—	9.83	133	96	10	3712	111.4	442	—	0.79
4 11, F 1.62	PDA	97	11.2	11.5	3.05	3.18	102	138	18	3962	91.6	320	2234	1.42
5 22, M 1.72	VSD	84	13.4	14.8	3.10	5.45	98	100	8	2657*	72.8	359	1500	1.19
		138	15.6	11.3	—	7.54	12	91	4	2717	74.3	496	—	0.66
6 13, F 1.43	VSD	81	8.6	10.4	3.20	8.16	98	60	8	1633	64.7	463	1034	0.78
7 25, M 2.04	CAo	90	10.6	11.7	4.18	—	75	94	16	2300	67.0	389	878	1.04
		117	13.5	11.6	6.70	—	105	110	—	4742	91.4	445	641	0.94
8 39, F 1.42	CAo	112	10.5	9.4	3.58	—	76	132	14	3144	76.1	215	2077	1.28
		153	17.3	11.3	4.80	—	100	147	12	4345	91.4	238	1725	0.96
9 36, F 1.49	CAo	131	16.8	12.8	3.01	—	86	133	13	4013	58.5	153	2319	1.02
		190	19.5	13.0	4.62	—	118	140	13	4774	70.0	208	1627	0.93
Congenital heart disease														
Mean resting values		101	12.0	11.8	3.46	5.72	92	106	12	2985	71.6	302	1657	1.04
Mean exercising values		138	16.2	11.8	5.37	7.10	123	114	9	3779	80.4	351	1331	0.82
Normal subject														
Mean resting values		82	8.5	10.4	3.23	3.23	77	93	9	1865	53.4	263	1347	1.14
Mean exercising values		113	12.6	11.1	5.09	5.09	99	99	12	2466	70.9	314	912	0.90
Significance of differences (congenital patients and normal subjects)														
Rest		< .003	< .001	< .03	< .3	< .001	< .03	< .2	< .2	< .005	< .01	< .5	< .2	< .3
Exercise		< .02	< .01	< .3	< .7	< .005	< .005	< .1	< .3	< .001	< .5	< .8	< .1	< .3

Abbreviations: BSA, Body surface area, M.²; PDA, patent ductus arteriosus; VSD, ventricular septal defect; CAo, coarctation of the aorta; CBF, coronary blood flow, ml./100 Gm. LV/min.; MVO₂, myocardial oxygen consumption, ml./100 Gm. LV/min.; C(A-V)O₂, coronary arteriovenous oxygen difference, volumes %; $\dot{Q}F$, forward LV flow index, L./min./M.² (also equals systemic flow index); $\dot{Q}T$, total LV flow index, L./min./M.² (also equals pulmonary flow index); LVed, left ventricular end-diastolic pressure; PTM, pressure-time integral, mm. Hg sec./min.; Stroke work index, Gm.M./beat/M.²; MSER, mean systolic ejection rate, ml./sec.; TPR, total peripheral resistance, dynes sec./cm.⁵; CRI, coronary resistance index, mm. Hg/ml./100 Gm. LV/min.

*Resting value.

†Exercising value.

body oxygen consumption and the systemic arterial mixed venous oxygen difference The oxygen content in the pulmonary artery was taken as the average of specimens from the main right and left pulmonary arteries The oxygen contents in the right ventricle right atrium and great veins were each obtained as the average of two or more specimens. Immediately before and after each measurement of CBF arterial and coronary sinus blood samples were obtained for the determination of lactate and pyruvate [19, 20]

Myocardial oxygen consumption (MVO_2) in milliliters per 100 Gm of left ventricle (LV) per minute was calculated as the product of CBF in milliliters per 100 Gm of LV per minute and the coronary arterial venous oxygen difference (C[A V]) determined from blood specimens drawn during the sixth minute of N_2O washout Excess lactate was calculated according to the Huckabee formula [21] The pressure-time per minute (PTM) in mm Hg-sec. per minute was calculated as the product of heart rate and the planimetrically or electrically integrated systolic arterial pressure recorded at paper speeds of 50 or 100 mm per second Stroke work, in gram meters per square meter of body surface area, was calculated as (MLVS-LVed) (SVI) (1 36)/100 where MLVS equals mean left ventricular systolic pressure LVed is left ventricular end-diastolic pressure (millimeters of Hg) and SVI is the stroke volume index (milliliters per beat per square meter) In the presence of a left to-right shunt work was calculated as the product of total stroke volume index and (MLVS-LVed) (1 36)/100 This represents work actually *generated* by the left ventricle which exceeds the stroke work delivered to the systemic circulation by the fraction of total stroke work lost in transmission across the defect. The mean rate of systolic ejection from the left ventricle (MSER milliliters per second) was calculated by dividing stroke volume by the systolic ejection period

A group of age-matched normal subjects over 13 and under 42 years of age studied at rest and during exercise and previously reported from our laboratories served as controls.[11, 22] Statistical analyses were performed using conventional techniques for small samples. Differences were evaluated by Student's t test. Correlations were measured using the correlation coefficient r

Results

The results of this study appear in Table I

Coronary and systemic hemodynamics at rest The mean values for CBF and MVO_2 were significantly greater in the patients with congenital heart disease than in the normal subjects and in each patient the observed CBF and MVO_2 equalled or exceeded the mean normal value. The C(A V) was also significantly greater than normal Thus an increased myocardial oxygen demand was met by increases in both flow and extraction The elevated MVO_2 was associated with a significantly more rapid mean heart rate a greater mean PTM and a larger mean total stroke work index (Table I) Moreover the mean pressure time per beat was significantly greater than that for normal subjects (33 0 versus 24 3 mm Hg-sec $p < 0.05$) demonstrating that the faster heart rate was not the only factor responsible for the larger PTM Mean arterial pressure and forward flow ($\dot{Q}_f$) were insignificantly different from values obtained in normal subjects. The patients with PDA (Table I Nos. 1 through 4) had pulmonary systemic flow ratios of 1 30 1 20 1 71 and 1 70 to one respectively and the patients with VSD (Nos 5 and 6) had ratios of 1 8 and 2 6 to one respectively In these patients forward flow ($\dot{Q}_f$) is equivalent to effective systemic blood flow and total left ventricular output ($\dot{Q}$) is equivalent to pulmonary blood flow (Table I) The MSER was not significantly different from normal and the mean values for both total peripheral and coronary resistances were within normal limits. As in the normal subjects, there was no excess lactate production None of the above results was altered by excluding Patient 4 who had systemic hypertension as well as a patent ductus both prior to catheterization (160/100) and during the study (174/113)

Coronary and systemic hemodynamics during exercise Those variables which were above normal at rest in patients with congenital heart disease were also supernormal during exercise. Patients with congenital

patients with PDA (140 beats per minute $p < 0.01$) and was more than two standard deviations above the mean normal value in the single patient with the VSD (Table I). Despite the supernormal MVO the total stroke work was within normal limits in all groups.

Discussion

This study demonstrates that the hemodynamic overloading of congenital heart disease results in an increased myocardial oxygen demand per unit of myocardium which is met by an elevated coronary blood flow and a normal or increased oxygen extraction. The increased myocardial oxygen consumption was uniformly associated with an elevated pressure time per minute but was independent of external work and not significantly related to any other hemodynamic variable studied. These findings are consistent with those which we have previously reported in patients with mitral stenosis.[14] However the absence of a significant correlation between the percentage changes in myocardial oxygen usage and in hemodynamic variables, from rest to exercise, suggests the importance of determinants which we did not measure such as wall tensions and contractile state. Estimation of wall tension requires knowledge not only of pressure but also of chamber volumes, which we did not measure. Sonnenblick and his associates, investigating the velocity of contraction as a determinant of oxygen consumption found that, during sustained postextrasystolic potentiation or norepinephrine or calcium infusion increases in oxygen demand were highly correlated with augmented rates of left ventricular ejection even when the PTM declined. The lack of correlation in this study between myocardial oxygen demand and mean systolic ejection rate would suggest that changes in the rate of fiber shortening or in contractility (the velocity-force-length relationship) are the more important variables, as has recently been suggested by Sonnenblick and co-workers.[22]

It has been demonstrated by Mosher and associates[23] who studied the control of coronary blood flow in dogs attached to an extracorporeal circuit which permitted variation of the coronary perfusion pressure, that as long as coronary perfusion pressures are adequate, arterial pressure did not appear to be a major determinant of coronary blood flow. The fact that coronary blood flow in the present study correlated better with myocardial oxygen requirements ($r = 0.88$) than with perfusion pressure ($r = 0.51$) and the failure to find a correlation between changes in coronary blood flow and changes in perfusion pressure with exercise suggests that coronary blood flow is autoregulated at a level related to myocardial effort and oxygen demand in the physiologic range of arterial pressure.

It is of interest that, in both pressure overloads and so-called volume overloads increases in myocardial oxygen consumption regardless of the level of $\dot{Q}_1$ and $\dot{Q}$ occurred only with increase in PTM which is a reflection of the pressure burden sustained by the left ventricular myocardium per unit of time. Alella and his associates have pointed out in animal studies that acute changes in volume flows correlate poorly with changes in MVO_2, but that associated pressure changes correlate well. This would therefore suggest that in the shunt lesions, the stimulus which results in increased metabolic demand is best described as a pressure overload.

Normal coronary flow (using the nitrous oxide technique) and myocardial oxygen consumption per unit of heart weight have been reported in patients in congestive heart failure.[26] In addition Rowe and his associates[31] found normal coronary flow (also by the nitrous oxide technique) and myocardial oxygen consumption in patients with severe aortic stenosis and regurgitation. However their study population consisted of severely symptomatic patients with aortic valvular disease being considered for surgery. Considering the nature and severity of their symptoms, all of these patients probably had myocardial failure. From the present study we would speculate that normal values for myocardial oxygen consumption in such patients represent a reduction from supernormal levels existing prior to the onset of myocardial failure. It has been demonstrated that contractility is an important determinant of oxygen consumption.[4-12] In addition we have demonstrated that myocardial contractility expressed as the maximum rate of

heart disease had a significantly higher mean CBF and MVO_2 and again in each patient the observed value for both variables exceeded the mean normal value. There was also a significantly greater PTM and more rapid heart rate, while MSER, coronary resistance index, $\dot{Q}_T$, mean arterial pressure, and total peripheral resistance did not differ from normal (Table I). Excess lactate production was not observed. Total stroke work, PT/beat, and C(A-V) were above normal during exercise but the differences did not achieve statistical significance. The LVed decreased or was unchanged in all patients in whom the measurement was made during exercise (Table I).

Determinants of coronary blood flow and myocardial oxygen consumption. For the pooled data at rest and during exercise, coronary blood flow correlated best with MVO_2 ($r = 0.88$, $p < 0.001$) but also exhibited significant correlations with aortic mean and diastolic pressures ($r = 0.51$ for both, $p < 0.05$). When hypertensive Patient No. 4, who was studied only at rest, was eliminated from the analysis, the correlation with aortic mean and diastolic pressures improved ($r = 0.64$ and $r = 0.63$, respectively, $p < 0.01$). Myocardial oxygen consumption exhibited a significant correlation with PTM ($r = 0.67$, $p < 0.01$). When hypertensive Patient No. 4 was eliminated from the analysis this correlation also improved ($r = 0.75$, $p < 0.001$). No significant correlation existed between MVO_2 and aortic pressures, stroke work, minute work, MSER, $\dot{Q}_L$, or $\dot{Q}_T$. During exercise, increments in MVO_2 (mean increase 31 per cent) were uniformly associated with increments in PTM (mean increase 25 per cent). Pressure time per beat changed little in any patient (mean change −9 per cent). Thus the increase in PTM during exercise was mediated entirely through the heart rate response. However, no significant correlations existed between the percentage change from rest to exercise in any of the measured variables and the percentage change in MVO_2 or CBF, indicating that factors other than those evaluated in this study were also important in determining the altered MVO_2 and CBF during exercise.

Analysis of subgroup data. At rest, the group of patients with PDA in which $\dot{Q}_L$ was significantly above normal (mean 5.18 L. per minute per square meter, $p < 0.02$) but mean aortic pressure was not (105 mm Hg, $p < 0.1$) had significant elevations of CBF (103 ml./100 Gm. of LV per minute, $p < 0.01$) and of MVO_2 (12.2 ml./100 Gm. of LV per minute, $p < 0.005$). Similarly, in CAo, with increased mean aortic pressure (120 mm Hg, $p < 0.05$) but normal ventricular output ($\dot{Q}_L$ 3.60 L. per minute per square meter, $p > 0.05$), the coronary blood flow (111 ml./100 Gm. of LV per minute, $p < 0.05$) and MVO_2 (12.6 ml./100 Gm. of LV per minute, $p < 0.05$) were significantly above the mean normal values. Heart rate was above normal in the PDA group (100 beats per minute, $p < 0.05$) but normal in CAo (79 beats per minute, $p < 0.7$). PTM was above normal in both groups (3,272 mm Hg-sec. per minute in PDA and 3,162 mm Hg-sec. per minute in CAo, both $p < 0.05$) as was PT per beat (33.6 and 39.7 mm Hg-sec. per beat, respectively, $p < 0.05$ for both). From these data it would appear that either a pressure overload or a so-called volume overload will be associated with increased MVO_2 if PTM is elevated, irrespective of heart rate and $\dot{Q}_L$. This impression is borne out by the data in the two patients with VSD. In one of these, despite appreciable elevation of heart rate and a $\dot{Q}_L$ over twice the normal mean ventricular output, PTM was slightly less than the mean value observed in normal subjects and MVO_2 differed minutely from the normal mean. In the other patient, with the same heart rate and $\dot{Q}_T$ and a smaller $\dot{Q}_L$, PTM and MVO_2 were comparably and substantially elevated above the mean values observed in normal subjects (Table I).

During exercise a supernormal MVO_2 was observed in patients with PDA (15.9 ml./100 Gm. of LV per minute, $p < 0.05$) and CAo (16.8 ml./100 Gm. of LV per minute, $p < 0.05$) and was associated, as it has been at rest, with a significant elevation in the PTM (3,573 mm Hg-sec. per minute, $p < 0.02$ in PDA and 4,287 mm Hg-sec. per minute, $p < 0.01$ in CAo). The heart rate during exercise did not differ from the normal mean in patients with CAo (108 beats per minute, $p > 0.15$), was significantly above the normal mean in

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Giant right atrium in rheumatic mitral stenosis

Atrial enlargement restricted by mural calcification

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In most patients with rheumatic mitral stenosis or regurgitation some degree of left atrial enlargement is evident, and when the left atrium becomes greatly dilated, the right atrial chamber is usually also quite large, even though the tricuspid valve leaflets and chordae tendineae may be anatomically normal. Enormous dilatation of the right atrium with only slight and quite disproportionate enlargement of the left atrium has not been reported in patients with acquired mitral valve disease. These were the unusual findings, however, in 3 patients recently studied by us. A description of the clinical and pathologic observations in these three patients is presented in the report which follows.

Patients studied

Pertinent clinical and necropsy features in the 3 patients are summarized in Table I. All had histories of acute rheumatic fever and long-standing symptoms of cardiac dysfunction. In each, mitral commissurotomy had been performed 6 to 9 years previously. Left atrial thrombi had been encountered at mitral commissurotomy in Patients Nos. 1 and 2, but none had had a systemic embolus. Before commissurotomy, Patients 1 and 2 had pure mitral stenosis. Patient No. 3, in addition to severe mitral stenosis, had a blowing systolic murmur compatible with tricuspid regurgitation, although there was no jugular venous distention, hepatomegaly, ascites, or subcutaneous edema. This patient had had this murmur at least since he was 19 years old, at which time he was suspected of having a pulmonary embolus. Angiography at that time, in addition to showing poor filling of the pulmonary arteries to the lower lobes, also showed a hugely dilated right atrium and a normal sized left atrium. Mitral commissurotomy was performed at age 33, and a systolic thrill was palpated over the right atrium at that time.

Each of the 3 patients was improved by mitral commissurotomy, but symptoms of cardiac dysfunction recurred two (Patients 1 and 3) to nine years (Patient 2) later. Severe right-sided congestive cardiac failure with dependent subcutaneous edema, ascites, pleural effusion, a large and pulsatile liver, and progressive deterioration occurred in each patient, almost certainly the result of restenosis of the mitral valve and concomitant development or worsening of tricuspid regurgitation. Precordial murmurs typical of tricuspid regurgitation were

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Table I Giant right atrium and nearly normal sized left atrium in mitral stenosis

Patient	Age, sex	Length of symptoms (yr.)	Cardiac valvular lesions	ECG	Age at cardiac cath. (yr.)	PA	Pressures (mm. Hg): RV†	RA	LA	LV†	SA	LA-LV mean gradient	CO/CI	Heart weight (Gm.)
1, M. V. A63-36	57, F	24	MS TR	AF RVH	57		82/15	m13 v22	m19 v29	118/12	118/61	8	4.6/3.1	880
2, E. L. A65-149	32, F	11	MS TR*	AF RVH	21	53/25	60/7	m4 v6	m17 v23		120/65		3.2/1.9	360
					23	30/20	30/4		m15 v22	96/6	116/72	5	3.6/2.0	
					32	55/41	60/17	m33 36	m34				3.3/1.3	
3, J. S. JHH [illegible]	39, M	26	MS TR	AF RVH RBBB	19	73/15	73/0				125/82			
					33	64/22	72/0	m9 v15	v25	125/5	135/85	13	3.4/2.0	[illegible]
					38	82/32	81/12	m25 v33		118/8	122/79		6.0/3.8	

Abbreviations: Cath, Catheterization; PA, pulmonary artery; RV, right ventricle; RA, right atrium; LA, left atrium; LV, left ventricle; SA, systemic artery; CO, cardiac output; CI, cardiac index; MS, mitral stenosis; TR, tricuspid regurgitation; AF, atrial fibrillation; RVH, right ventricular hypertrophy; RBBB, right bundle branch block; m, mean, v, v wave.
*TR was not present before mitral commissurotomy.
†Systolic and end diastolic pressures.

audible in each patient after the recurrence of symptoms of cardiac dysfunction. Reoperation was carried out in patients. In Patient 1 the tricuspid valve was replaced, another mitral commissurotomy was performed, and a portion of the redundant right atrial wall was resected. In Patient 3 the mitral valve was replaced and a tricuspid annuloplasty performed. In both patients severe tricuspid regurgitation was evident at operation. Patient No. 2 died before reoperation was performed. Patient No. 1 died 10 days postoperatively of inadequate cardiac output, probably the result of operatively induced mitral regurgitation, and Patient No. 3 died 4 months postoperatively from consequences of prosthetic mitral stenosis resulting from interference to ball movement by the left ventricular wall.

Necropsy in each patient disclosed a large heart, an enormous right atrium, a mildly dilated left atrium, diffuse calcific deposits of the left atrial and atrial septal walls, and mitral valve leaflets, but no calcification of the right atrial walls. The tricuspid valve leaflets and chordae tendineae were thickened and fibrous in each patient. All 3 patients had extensive pulmonary vascular and parenchymal changes, and congestion of all viscera, including severe centrolobular hepatic necrosis, hemorrhage, and fibrosis. Various clinical and necropsy findings of particular interest are illustrated in Figs. 1 through 7.

Discussion

Extreme, enormous, or giant-sized dilatation of the left atrium (probably greater than 1,000 ml. capacity; normal less than 150 ml. [4]) has been discussed for years. [4-] These reports indicate that enormous left atrial dilatation nearly always occurs in patients with mitral valvular disease. The mitral lesion may be pure regurgitation, pure stenosis, or a combination of the two, and there is some controversy as to which of these functional alterations is most frequently associated with a giant-sized left atrium. Also, the reason that one patient with mitral dysfunction has a huge left atrium and another with a similar functional abnormality has only minimal left atrial dilatation has not been resolved.

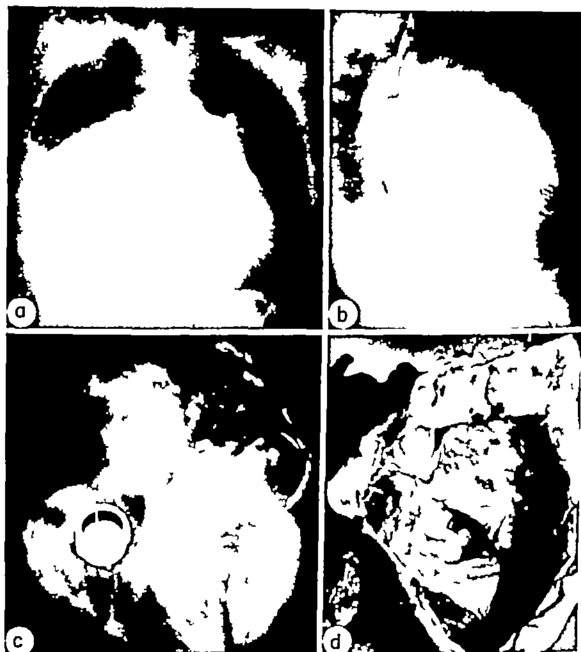


Fig 1 Patient 1 (Table I). a and b Chest roentgenograms taken 3 weeks before death The huge right atrium forms the right border of the heart on the posteroanterior view c Radiograph of the heart specimen. The left atrial wall is calcified. Much of the right atrial wall was excised at operation. The tricuspid valve was replaced with a Starr Edwards prosthesis and a mitral commissurotomy was also done. d Opened left atrium showing its calcified wall which also is focally covered by thrombi.

Nearly all patients with enormous left atria have histories of acute rheumatic fever or chorea and it has been suggested that they have more severe attacks of or more relapses of acute rheumatic fever than do patients with similar valvular lesions and less left atrial dilatation Since rheumatic fever always involves the left atrial wall it is reasonable to speculate that if the inflammatory process was severe or occurred repeatedly the atrial wall would be more damaged consequently more compliant or elastic and therefore more easily dilated by increased intra-atrial pressure. Although nearly all patients with chronic rheumatic mitral disease have abnormal left atrial walls the degree of myocardial destruction and fibrosis appears to be far worse in the subjects with dilated left atria than in those with smaller sized chambers

Patients with giant-sized left atria and

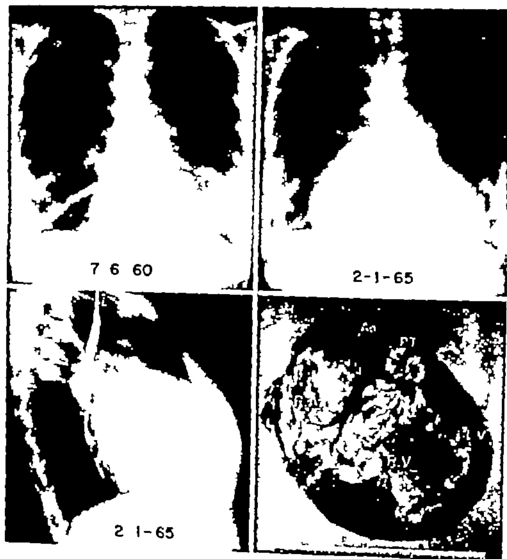


Fig. 2. Patient No. 2 *Upper* and *lower left.* Chest roentgenograms taken on the dates show The patient died Aug 13, 1965 *Lower right* Anterior surface of heart. The left trium is not isible anteriorly but the right trium (*R. 1.*) is ery large *R.1* Right entricle *L.V* left entricle *P.T* pulmonary trunk *A* aorta.

severe m tr l valvular d sease usually have only slightly elevated or even normal left at ial pulmonary venous, pulmonary ar terial nd ght ventricular pressures.[19] In contrast these pressu es are usually qu t high in ul jects w th only mildly dilated or normal sized left atria and severe mitral alvular disease The small left atrium is less ompliant, and reflects its elevated pressure to the lung and to the right ven t icle whereas the hugely dilated left atrium is readily compliant and absorbs" th pressure energy In most patients with giant left atrium the right atrium is also dilated but is never as large as the left [4] Right atrial d latation occurs as the result of tricuspid regurgitation which may be either organic or functional in type and w th or without accompanying tricuspid stenosis. Stretch ng of the atrial septum by the dilatation of the left atrium probably contributes to the d latation of the right atrium also.

Many reports have described the oc currence of giant left atrium in patients w th m tral al ular disease but the oc

Fig 3 Heart in Patient No 2 *a* and *b* were photographed at the same magnification In *a* the huge right atrium has been partially opened showing the dilated tricuspid valve orifice (*T V.O*) and in *b* the only slightly dilated left atrium has been partially opened showing the stenotic mitral valve orifice (*M V O*). *c* and *d* likewise were taken at the same magnification and show a huge right atrium (*R.A*) in *c* compared to an only slightly dilated left atrium (*L.A*) in *d*. The left atrial wall contains many deposits of calcium. The tricuspid leaflets are only slightly thickened not enough in themselves to account for the tricuspid regurgitation.

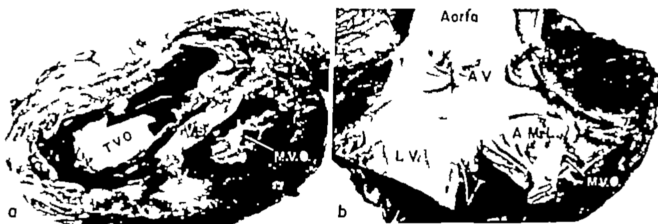


Fig 4 Heart in Patient No. 2. *a* The caudal portions of the ventricles have been removed. The right ventricular cavity is much larger than the left, and the mitral valve orifice (*M V.O*) is severely stenotic. The tricuspid valve orifice (*T V.O*), in contrast, is greatly dilated. *b* Opened aorta, normal aortic valve (*A V*) and left ventricular outflow tract (*L V*) The mitral leaflets insert directly into the papillary muscles. The cause of the left ventricular dilatation is uncertain. *A.M.L.*, Anterior mitral leaflet.



Fig. 5. Chest roentgenograms in Patient No. 3 taken 5 months before death.

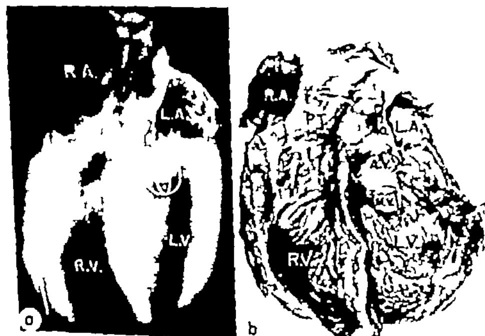


Fig. 6. Heart of Patient No. 3. *a*, Radiograph of excised heart, showing large calcific deposit in the left atrial (*L.A.*) wall. The mitral valve has been replaced with a Starr-Edwards prosthesis. *R.A.*, Right atrium; *R.V.*, right ventricle; *L.V.*, left ventricle. *b*, Opened right ventricle, pulmonary trunk (*P.T.*), left ventricle (*L.V.*), aortic valve (*A.V.*), and aorta ([illegible]). Both ventricles are greatly enlarged. *M.V.*, Mitral valve prosthesis.

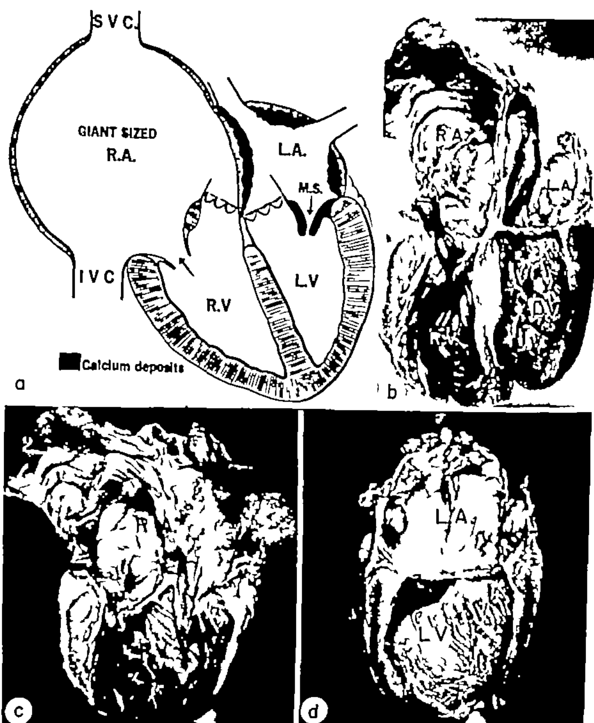


Fig 7 Heart of Patient No. 3 *a* Diagram. *S V C*, Superior vena cava *I V C* inferior vena cava *R.A* right atrium *R.V.*, right ventricle *L.A* left atrium *M S* mitral stenosis and *L.V* left ventricle. *b* Longitudinal section of heart again showing the calcified left atrial wall and the huge right atrium. *c* and *d* are taken at the same magnification. *c*, Opened right atrium and right ventricle and *d* opened left atrium and left ventricle. The mitral prosthesis has been removed.

currence of a giant sized right atrium with only a slightly dilated left atrium has not been specifically described Taussig[11] noted enormous (capacity 2 150 ml) dilatation of the right atrium and a normal sized (capacity 100 ml) left atrium in a 43 year old woman with mitral and tricuspid stenosis and regurgitation probably of rheumatic etiology although the patient may have had the Marfan syndrome The left atrial wall was free of calcific deposits and the heart weighed 505 grams. The cause of this unusual type of atrial dilatation is unknown

In each of the 3 present patients the left atrial wall was calcified the left atrium was only mildly dilated, but the right atrial cavity was huge The hemodynamic and anatomic findings suggest that the calcium deposits in the left atrial wall prevented this chamber from dilating decreased *its compliance and caused the elevated left* atrial pressure to be immediately reflected to the pulmonary vessels and right ventricle leading to tricuspid regurgitation of progressive severity It seems likely that the calcification of the left atrium was the result of organization of thrombi and in two of the patients thrombi were found at the initial operation Each of the three patients had severe nearly pure mitral stenosis. Had significant or pure mitral regurgitation been present it appears unlikely that left atrial thrombi would have formed since significantly sized left atrial thrombi have not been found in our experience in patients with severe mitral regurgitation

Summary

Attention is called to the occurrence of a giant-sized right atrium and a nearly normal-sized left atrium in 3 adult patients with rheumatic mitral stenosis. In each patient the left atrial wall was calcified probably the result of organization of intra atrial thrombus, and the calcific deposits prevented the left atrium from dilating All patients also had tricuspid regurgitation, which certainly contributed to the development of enormous right atrial dilatation although other undetermined factors were probably operative also

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Ultrasonic determination of left ventricular wall motion in normal man

Studies at rest and after exercise

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Seattle Wash

In 1954 Edler and Hertz[1] first demonstrated that a strong ultrasonic echo could be obtained from the posterior wall of the left ventricle and that this echo had a characteristic pattern of motion during the cardiac cycle Amplified ultrasonic cardiograms (UCG) were depicted with simultaneously recorded electrocardiograms. In recent years the ability to obtain a discrete posterior wall (PW) echo in most individuals has been well accepted and has formed a basis for the use of ultrasound in the detection of pericardial effusion[2] However few investigators have utilized ultrasound to study posterior wall movement, although considerable attention has been given to the motion characteristics of the mitral valve echo[3,4] and the mitral ring echo[4,5] Since the posterior wall reflection is easily recorded and provides beat to beat information on ventricular position dimension and velocity of contraction[6,7] the further characterization and quantitation of PW motion may be useful This paper reports an analysis of ventricular wall motion in healthy adults studied at rest and immediately *after moderate exercise.* These values may be used subsequently as a standard with which to compare patients with heart disease

Methods

Twenty five healthy adult males, ages 20 to 46 were studied at rest in the supine position The examinations were performed with a commercially available ultrasonoscope (Ekoline 20 SK Instrument Co Philadelphia Pa) using a 2 25 megacycle, ½ inch diameter transducer that transmitted 1 μsec ultrasound impulses at a rate of 200 per second Reject and damping controls allowed for the obliteration of low intensity echos. Using a gel coupling medium the hand held transducer was placed in the fourth intercostal space adjacent to the left sternal border and directed posteriorly to obtain the posterior wall echo Near and coarse gain reject and damping modalities and the angle of the transducer were adjusted to obtain the clearest posterior wall signal as visualized on the

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A-scan mode on the oscilloscope. The moving echo was then located within a 4 cm time-analogue gate and the resultant signal amplified and inscribed on an Electronics for Medicine DR-8 photograph recorder. Amplification calibrations were made prior to each study with the use of a pure echo signal obtained from a plexiglass block, so that 4 cm. of excursion within the gating device produced 10 cm of displacement on the photographic recorder. The posterior wall movement was thereby amplified by a factor of 2.5. Simultaneous electrocardiographic (Lead II) recordings were made in all individuals. When the posterior wall echogram was as free as possible from low intensity noise, a recording was obtained at a paper speed of 50 mm. per second. In order to determine the distance between the transducer and posterior wall permanent Polaroid photographs were taken of the B-scan presentations, illustrated in Fig. 1.

Following resting recordings, each subject exercised by running in place for approximately three minutes. It was not the intent of the experiment to provide a constant, carefully measured work load but rather to present enough of an exercise stimulus to produce significant changes in heart rate. Following exercise, the subjects resumed the supine position and ultrasound recordings were repeated. Immediate postexercise recordings were difficult to obtain in some individuals because of hyperventilation. In five subjects satisfactory postexercise observations were not made.

Simultaneous recordings of the PW movement and left ventricular pressure have been made in a few patients undergoing cardiac catheterization. The record of one patient has been included in this report in order to illustrate the approximate timing of PW motion during the cardiac cycle.

All recordings of wall motion were analyzed in a similar manner. Calculations were performed on several beats at various stages of the respiratory cycle and then averaged. The total amplitude of the curve was measured to obtain posterior wall excursion (PWE). The maximal posterior wall velocity (PWVM) was determined by drawing a tangent to the steepest point on the systolic limb of the curve and measuring the slope in centimeters per second. The mean posterior wall velocity (mean PWV) was measured as the slope of the line extending from the onset of anterior PW displacement to the peak of the echogram. An estimate of electromechanical systole was obtained by measuring the time from the Q wave of the ECG to the peak of the UCG (Q-D interval).

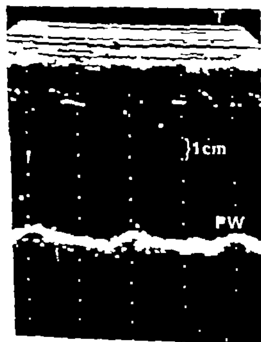


Fig. 1. B-presentation of the posterior wall echo (PW) in a normal subject. T represents the echo originating from the transducer. Time-distance dots indicate 1 cm vertically and ½ sec horizontally.

Results

A characteristic posterior wall motion curve was obtained in most individuals as illustrated in Fig. 2. To avoid a new denotation of time events, the letters follow those introduced by Edler and Gustafson[4] to describe the timing of mitral valve motion. Point B, the wall position at end diastole, is nearly synchronous with the R wave of the ECG. During isovolumetric contraction the wall moves in a posterior direction (BC) before its major motion anteriorly during systolic ejection (CD). In early diastole (EF) the posterior wall

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Methods

Twenty-five healthy adult males, ages 20 to 46, were studied at rest in the supine position. The examinations were performed with a commercially available ultrasonoscope (Ekoline 20, SK Instrument Co., Philadelphia, Pa.) using a 2.25 megacycle ¾ inch diameter transducer that transmitted 1 μsec ultrasound impulses at a rate of 200 per second. Reject and damping controls allowed for the obliteration of low intensity echos. Using a gel coupling medium, the hand held transducer was placed in the fourth intercostal space adjacent to the left sternal border and directed posteriorly to obtain the posterior wall echo. Near and coarse gain, reject, and damping modalities, and the angle of the transducer were adjusted to obtain the clearest posterior wall signal as visualized on the

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Table I. Posterior wall motion in normal subjects

Subject			Transducer PW distance (cm.)	HR (beats/min.)		PWE (cm.)		PWVM (cm./sec.)		Mean PWV (cm./sec.)		Q-D Interval (sec.)	
N	Sex	Age		Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
1	M	36	10.3	59	103	0.76	0.92	4.9	6.5	2.9	4.0	0.34	0.30
2	M	29	11.4	70	100	0.64	0.80	3.4	7.2	2.3	5.0	0.34	0.20
3	M	26	—	61	—	1.00	—	6.7	—	3.6	—	0.36	—
4	M	31	11.8	59	90	0.52	1.34	3.6	10.0	2.2	6.5	0.36	0.26
5	M	36	11.2	72	—	0.68	—	3.3	—	2.3	—	0.35	—
6	M	28	12.1	63	93	0.84	1.06	5.9	10.4	2.8	5.3	0.39	0.24
7	M	27	10.5	77	109	0.60	0.84	3.9	8.3	2.5	4.2	0.39	0.30
8	M	41	12.3	65	—	0.76	—	4.3	—	2.7	—	0.32	—
9	M	26	9.1	81	113	0.64	0.78	3.8	13.0	2.8	5.3	0.31	0.22
10	M	39	12.7	63	—	0.70	—	4.4	—	2.8	—	—	—
11	M	31	11.2	76	125	0.48	0.92	2.3	6.3	1.6	4.8	0.38	0.28
12	M	25	10.8	54	81	0.96	1.20	3.8	7.1	3.0	4.4	0.42	0.38
13	M	25	11.3	66	139	0.72	1.08	5.6	14.3	3.3	6.7	0.32	0.20
14	M	46	11.2	62	115	0.36	0.60	2.2	8.3	1.7	4.6	0.28	0.16
15	M	27	12.2	71	103	0.68	0.80	3.1	8.0	2.0	3.2	0.31	0.30
16	M	33	12.2	61	91	0.92	0.66	4.4	6.2	3.3	4.0	0.35	0.20
17	M	4	10.8	58	146	1.04	1.48	4.8	12.5	3.2	7.7	0.38	0.24
18	M	34	11.2	77	115	0.64	1.16	4.6	9.1	2.	5.3	0.30	0.28
19	M	28	11.2	65	84	0.52	0.44	2.6	5.9	1.5	2.9	0.34	0.26
20	M	31	11.1	63	94	0.64	1.04	4.2	8.3	2.6	5.6	0.36	0.32
21	M	30	11.2	58	107	0.80	1.08	4.4	12.5	3.1	7.2	0.36	0.22
22	M	25	10.2	63	107	0.80	1.00	3.2	5.5	2.5	4.3	0.39	0.26
23	M	20	10.3	81	—	0.60	—	4.8	—	3.6	—	0.24	—
24	M	28	11.8	55	103	0.76	0.92	4.0	14.3	2.8	5.9	0.32	0.22
25	M	24	10.8	57	111	1.03	1.24	4.9	10.0	3.2	6.7	0.38	0.26
Mean			11.2	66	106	0.72	0.96	4.1	9.2	2.7	5.2	0.34	0.25
± 1 S.D.			±0.82	±8	±17	±0.18	±0.25	±1.1	±2.8	±0.58	±1.3	±0.04	±0.05

Abbreviations: HR, heart rate; PWE, posterior wall excursion; PWVM, maximal posterior wall velocity; PWV, posterior wall velocity.

increased with exercise to 106 ± 17 beats per minute (66 per cent). In this group the PWE was 0.72 ± 0.18 cm at rest and 0.96 ± 0.25 cm following exercise (33 per cent). Exercise produced an increase in PWVM from 4.0 ± 1.0 to 9.2 ± 2.8 cm per second (130 per cent). The mean PWV also increased from 2.6 ± 0.36 to 5.2 ± 1.3 cm per second (100 per cent). At rest the Q-D interval was 0.35 ± 0.04 sec and decreased to 0.25 ± 0.05 sec. (28 per cent) following exercise. These changes are shown in Figs. 4 and 5. It is apparent that the mean and maximal PWV increased and that the Q-D interval decreased in every individual after exercise. The posterior wall amplitude was greater in all but two subjects in the postexercise state. The Student paired t test revealed the mean of the change in each variable to be highly significant ($p < 0.001$).

The change in heart rate (ΔHR) was compared with changes in PWVM, mean PWV, and PWE for each subject. There was only a fair but significant correlation between ΔHR and ΔPWVM ($r = 0.48$, $p < 0.05$). This relationship is shown in Fig. 6. A poorer relationship was noted between ΔHR and Δ mean PWV ($r = 0.42$, $p > 0.01$). There was no significant correlation between ΔHR and ΔPWE ($r = 0.3$, $p > 0.1$). The correlation between HR and wall excursion in resting individuals is shown in Fig. 7 ($r = -0.49$, $p < 0.05$). It can be seen that the heart rate varied

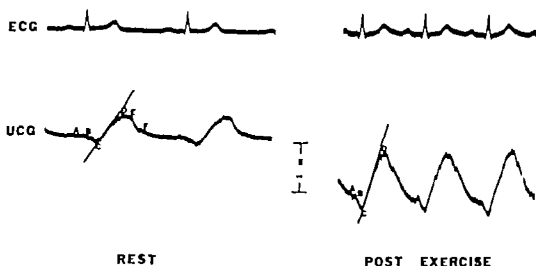


Fig. 2. The normal ultrasonic pattern of posterior wall motion (UCG) recorded simultaneously with the electrocardiogram (ECG) at a paper speed of 50 mm. per second. Analogue tracing at rest and after moderate exercise are shown. The lettering is explained in the text. The vertical scale indicates 1 cm. of wall excursion. An upward movement in the tracing represents a movement toward the anterior chest wall. The drawn tangents illustrate the determination of maximal wall velocity.

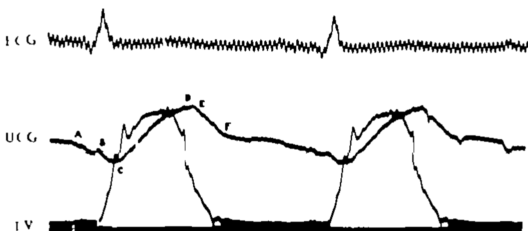


Fig. 3. Analogue ultrasound recording of the posterior wall echo (UCG), electrocardiogram (ECG), and left ventricular pressure (LV) at a paper speed of 100 mm. per second. As the ventricular pressure rises during isovolumetric contraction, the wall moves posteriorly (BC). During left ventricular ejection, the wall moves toward the anterior chest (CD). After isovolumetric relaxation, the posterior wall returns to a more dorsal position (EF). These recordings are taken from a patient with coronary artery disease and normal hemodynamics at cardiac catheterization.

returns nearly to its base-line position. Point A corresponds to the onset of atrial contraction and in some individuals is followed by a gradual sloping posteriorly which is usually easy to distinguish from the more abrupt dip produced by isovolumetric contraction. Point F represents the end of isovolumetric relaxation just prior to rapid diastolic filling. These relationships are further clarified by a simultaneous recording of the UCG and left ventricular pressure (Fig. 3).

Following exercise (Fig. 2) both the slope of wall motion during systolic ejection and the total excursion of the curve increased. Table I tabulates data obtained in 25 subjects at rest and in 20 immediately after exercise. In all the resting subjects the transducer posterior wall distance ranged from 9.1 to 12.7 cm. with a mean of 11.2 ± 0.82 cm. In those 20 individuals in whom both rest and postexercise observations were made, the mean heart rate at rest was 64 ± 8 beats per minute and

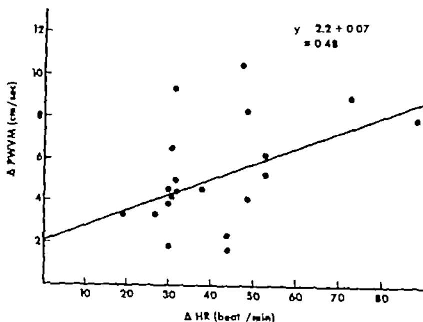


Fig. 6 Relationship of change in heart rate (ΔHR) t change in maximal posterior wall locity ($\Delta PWVM$) after moderate exercise.

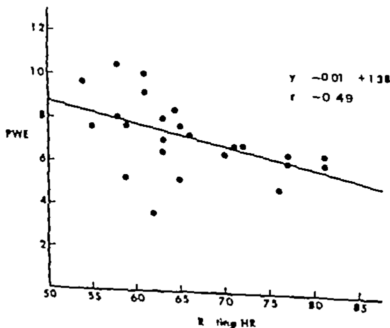


Fig. 7 Relationship of heart rate t posterior wall excursion (PWE) in resting subjects

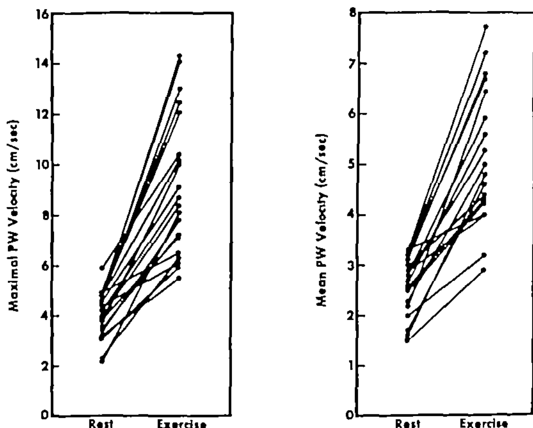


Fig 4 Posterior wall velocities at rest and after exercise. An increase in both maximal and mean PW velocity was observed for each subject ($p < 0.001$) represented by the interconnected closed circles.

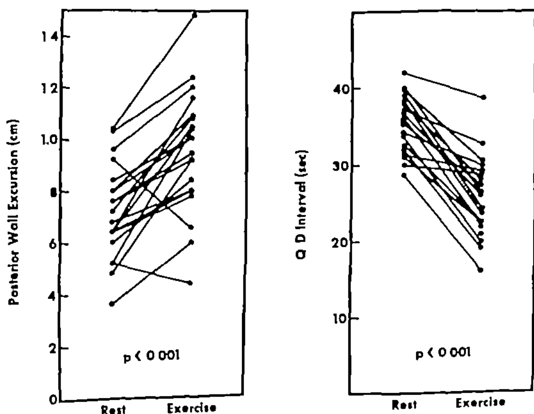


Fig 5 Posterior wall excursion and QD intervals at rest and following exercise Symbols as in Fig 4

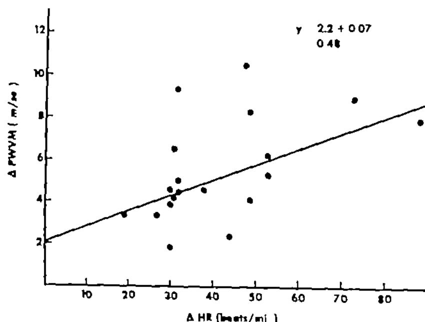


Fig. 6 Relationship of change in heart rate (ΔHR) to change in maximal posterior wall velocity ($\Delta PWVM$) after moderate exercise.

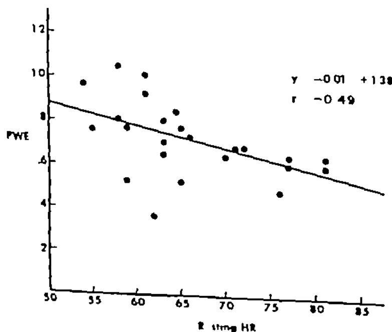


Fig. 7 Relationship of heart rate to posterior wall excursion (PWE) in resting subjects

inversely with the amplitude of wall movement

Discussion

Ultrasound cardiography provides a one dimensional view of ventricular wall motion during the cardiac cycle. Bowyer Crawford and Johns[7] demonstrated the feasibility of using ultrasound to record pressure-dimension loops of the left ventricular chamber in patients undergoing left heart catheterization Rushmer and co-workers[8] utilized direct sonocardiometry in dogs to record continuous changes in left ventricular diameter The transit time of sound waves between two barium titanate crystals mounted on opposing walls of the left ventricle was electronically monitored A curve morphologically similar to the posterior wall echogram shown here (Figs 2 and 3) was obtained It was noted that the sonocardiometry curve bore strong resemblance to the standard ventricular *volume curve This suggests that posterior* wall motion during the cardiac cycle may be considered a function of changing ventricular diameter and volume The amplitude of wall motion from end diastole to end systole might therefore be related to stroke volume Fig 7 demonstrates an inverse relationship between PW excursion and heart rate in resting subjects Assuming an approximately equal cardiac output in resting normals such a relationship is not unexpected Those individuals with slower *rates would have larger stroke volumes* and greater wall amplitude during systole Those with faster rates would have smaller stroke volumes and less wall excursion A similar observation was made by Zaky and associates[4] in a study of the mitral ring echo (MRE) The amplitude of ring motion varied directly with the body surface area and inversely with the heart rate, that is, directly *with the expected* stroke volume

The configuration of the posterior wall UCG deserves comment. It can be noted (Fig 3) that there is a small initial movement posteriorly (*BC*) during isovolumetric contraction During this phase of the cardiac cycle a change in the shape of the ventricle occurs.[9] The internal diameter and external circumference increase abruptly as the longitudinal axis of the chamber is shortened by contraction of the papillary muscles and trabeculae carnae. The lateral walls bulge outward so that the chamber assumes a more spherical configuration The initial posterior displacement of the PW therefore correlates with the known geometrical events of isovolumetric contraction During ventricular ejection there is a reduction in cross sectional diameter[9,11] and the posterior wall moves anteriorly (Fig 3 *CD*)

In this study maximal and mean posterior wall velocities have been calculated directly from the time-motion curve during systolic ejection It may be assumed that the rate of anterior motion of the PW echo is related to the rate of decrease in ventricular diameter and therefore to the velocity of circumferential fiber shortening Observations following moderate exercise demonstrate an average increase in maximal wall velocity of 130 per cent and in mean wall velocity of 100 per cent *(Fig 4) These results are in agreement* with studies by Sonnenblick and associates[12] in intact man which show that the exercise state induces an elevation of contractile velocity at any given ventricular pressure and dimension The small but relatively consistent increase in the amplitude of PW motion after exercise (Fig 5) suggests an absolute increase in myocardial fiber shortening an observation previously made with thermodilution technique[13] We suggest that ultrasonic *cardiography may be of use in assessing* changes in ventricular contractility

The correlation between change in posterior wall velocity and change in heart rate as displayed in Fig 6 was not high (r = 0 48) Frank and Levinson[14] calculated a contractility index (maximal ventricular dp/dt corrected for maximal isovolumetric pressure and end-diastolic *dimension) in 16 patients with normal* left ventricles. Rest and exercise observations were made and a high correlation (r = 0 76) was found between increments in contractility and increments in heart rate The nature of our study precluded correction for several variables, including end-diastolic volume and afterload which may account for the poorer correlation Nevertheless, both studies indicate a close relationship between the inotropic

and chronotropic stimulation of exercise.

Another parameter measured was the time interval between the onset of the QRS and the peak of the motion curve (Q-D interval). Point D represents the instant when the PW ceases to move anteriorly and thus coincides closely with the end of systolic ejection. The Q-D interval, therefore, is an estimate of total electromechanical systole. This analysis may be in error if other dimensions of the ventricle continue to change after PW movement has stopped or if the heart swings posteriorly within the chest cavity during ejection. This may explain the fact that mean systole measured in this manner (0.340 sec.) at a mean heart rate of 66 was somewhat shorter than total systole (0.407 sec.) predicted from the regression equation presented by Weissler and associates.[15] Since the pre-ejection period and ejection time are more sensitive indicators of cardiac dysfunction than total electromechanical systole,[14] it might be possible to estimate these intervals from the simultaneously obtained PW motion curve and ECG. Correlation between estimations made in this manner and more conventional methods of measuring time events was not done in this study but would be of interest.

Summary

The analogue presentation of the echocardiogram was used to measure parameters of left ventricular wall motion in 25 normal males at rest and in 20 individuals after moderate exercise. Characteristic tracings of posterior wall motion recorded by this technique are discussed with relation to ventricular pressure and geometric events during the cardiac cycle. Following exercise significant increases ($p < 0.001$) in posterior wall excursion and velocity were evident with only a fair correlation ($r = 0.48$) between increments in maximal wall velocity and heart rate. It is suggested that measurements of posterior wall motion with reflected ultrasound may provide an innocuous means of assessing changes in ventricular contractility.

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inversely with the amplitude of wall movement

Discussion

Ultrasound cardiography provides a one dimensional view of ventricular wall motion during the cardiac cycle Bowyer Crawford and Johns[7] demonstrated the feasibility of using ultrasound to record pressure-dimension loops of the left ventricular chamber in patients undergoing left heart catheterization Rushmer and co-workers[8] utilized direct sonocardiometry in dogs to record continuous changes in left ventricular diameter The transit time of sound waves between two barium titanate crystals mounted on opposing walls of the left ventricle was electronically monitored A curve morphologically similar to the posterior wall echogram shown here (Figs 2 and 3) was obtained It was noted that the sonocardiometry curve bore strong resemblance to the standard ventricular volume curve This suggests that posterior wall motion during the cardiac cycle may be considered a function of changing ventricular diameter and volume The amplitude of wall motion from end diastole to end systole might therefore be related to stroke volume Fig 7 demonstrates an inverse relationship between PW excursion and heart rate in resting subjects. Assuming an approximately equal cardiac output in resting normals such a relationship is not unexpected Those individuals with slower rates would have larger stroke volumes and greater wall amplitude during systole Those with faster rates would have smaller stroke volumes and less wall excursion A similar observation was made by Zaky and associates[4] in a study of the mitral ring echo (MRE) The amplitude of ring motion varied directly with the body surface area and inversely with the heart rate, that is directly with the expected stroke volume.

The configuration of the posterior wall UCG deserves comment. It can be noted (Fig 3) that there is a small initial movement posteriorly (*BC*) during isovolumetric contraction During this phase of the cardiac cycle a change in the shape of the ventricle occurs.[9] The internal diameter and external circumference increase abruptly as the longitudinal axis of the chamber is shortened by contraction of the papillary muscles and trabeculae carnae. The lateral walls bulge outward so that the chamber assumes a more spherical configuration The initial posterior displacement of the PW therefore correlates with the known geometrical events of isovolumetric contraction During ventricular ejection there is a reduction in cross sectional diameter[9, 11] and the posterior wall moves anteriorly (Fig 3 *CD*)

In this study maximal and mean posterior wall velocities have been calculated directly from the time motion curve during systolic ejection It may be assumed that the rate of anterior motion of the PW echo is related to the rate of decrease in ventricular diameter and therefore to the velocity of circumferential fiber shortening Observations following moderate exercise demonstrate an average increase in maximal wall velocity of 130 per cent and in mean wall velocity of 100 per cent (Fig 4) These results are in agreement with studies by Sonnenblick and associates[12] in intact man which show that the exercise state induces an elevation of contractile velocity at any given ventricular pressure and dimension The small but relatively consistent increase in the amplitude of PW motion after exercise (Fig 5) suggests an absolute increase in myocardial fiber shortening an observation previously made with thermodilution technique[13] We suggest that ultrasonic cardiography may be of use in assessing changes in ventricular contractility

The correlation between change in posterior wall velocity and change in heart rate as displayed in Fig 6 was not high ($r = 0.48$) Frank and Levinson[14] calculated a contractility index (maximal ventricular dp/dt corrected for maximal isovolumetric pressure and end-diastolic dimension) in 16 patients with normal left ventricles. Rest and exercise observations were made, and a high correlation ($r = 0.76$) was found between increments in contractility and increments in heart rate The nature of our study precluded correction for several variables including end-diastolic volume and afterload which may account for the poorer correlation. Nevertheless both studies in[illegible]cate a close relationship between t[illegible] c

after free interval of two months, there was recurrence of ventricular tachycardia in January 1968 complicated for the first time by congestive heart failure.

Pacemaker rhythm had to be restored by DC shock after an increase in the pacing rate to 125 per minute failed to terminate the arrhythmia. It was hoped that more effective prophylaxis would be attained by permanent pacing at 104 per minute instead of 96 per minute since relapse had occurred with the latter rate. However the more rapid pacing had to be abandoned because the patient could not tolerate the unpleasant palpitation. Therefore the pacing rate was diminished to 98 per minute, but the propranolol dosage was increased to 160 mg daily. Sodium restriction and intermittent diuretic therapy were added to the digoxin to avoid the precipitation of heart failure even in the absence of ventricular tachycardia, because of the increased dose of propranolol. On this medical regimen together with artificial cardiac pacing at 98 per minute she has now remained comfortable and active, free of arrhythmia and congestive heart failure for 14 months.

Patient 2. A 61 year-old man with previous myocardial infarcts was admitted to the hospital for treatment of an acute myocardial infarction complicated by congestive heart failure. On the seventh day he experienced 6 episodes of cardiac arrest due to ventricular tachycardia. The ventricular rate was 250 beats per minute. Serum potassium was 4.8 mEq. per liter. Rapid pacing was used to prevent recurrence of the arrhythmia because of the ineffectiveness of drug therapy including quinidine, procaine amide, lidocaine, and diphenylhydantoin. When attempts at trial pacing were unsuccessful, despite monitoring of the catheter position with the image intensifier the catheter was advanced into the right ventricle. With a pacing rate of 105 per minute there was no ventricular tachycardia. There was no evidence of retrograde conduction. The following morning when his pacing rate was slowed to 90, ventricular tachycardia recurred promptly. The arrhythmia could not be terminated by increasing the pacing rate to 120 and the stimulus from 3 to 12 volts. Following DC shock which terminated the arrhythmia, pacing was resumed at 120 per minute supplemented by procaine amide. However possibly because his congestive heart failure was not adequately controlled, he had three additional attacks of ventricular tachycardia despite continued pacing. The last episode could not be terminated by repeated DC shocks and the patient died.

Patient 3. A 63-year-old man with primary myocardial disease (subsequently confirmed at autopsy) was admitted to the hospital in congestive heart failure. The electrocardiogram revealed paroxysmal ventricular tachycardia, with ventricular rates between 136 to 150 beats per minute (Fig. 1). The arrhythmia did not respond to lidocaine but was temporarily suppressed by a sinus tachycardia of 130 per minute induced by atropine and isoproterenol.[17] There was no retrograde A-V conduction. In the hope that control of the arrhythmia would result in improved cardiac output, transvenous pacing was begun at 120 per minute supplemented by procaine amide one gram every 4 hours. At the

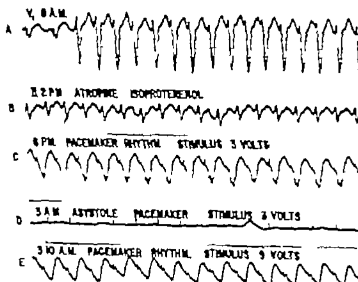


Fig. 1. *A*, Ventricular tachycardia (*VT*) uncontrolled by lidocaine. *B*, Suppression of *VT* by sinus tachycardia, 130 per minute, induced by intravenous atropine and isoproterenol. *C*, Transvenous pacing 120 per minute. *D*, Asystole after pacing 12 hours despite continued pacemaker stimulation. *E*, Pacemaker rhythm with pacing stimulus increased from 3 to 9 volts.

Suppression of refractory recurrent ventricular tachycardia by transvenous rapid cardiac pacing and antiarrhythmic drugs

Report of seven cases

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Recurrent ventricular tachycardia often complicated by ventricular fibrillation and independent of heart block or sinus bradycardia may present a serious and challenging therapeutic problem Scattered reports, usually of solitary cases have indicated that rapid artificial cardiac pacing may sometimes control these arrhythmias after they have proved refractory to drug therapy [1-14] We are reporting our experience in the management of a series of 7 successive patients with recurrent ventricular tachycardia and fibrillation None of these patients had coexistent heart block or bradycardia This group of patients is of particular interest because it provides a spectrum of clinical situations and varied therapeutic responses which demonstrate both the value and shortcomings of artificial rapid cardiac pacing

Case reports

Patient 1 A 59 year-old woman with healed diaphragmatic myocardial infarction experienced approximately 50 episodes of ventricular tachycardia between March and October 1967 The ventricular rates ranged between 180 to 200 beats per minute. The serum potassium was 4 7 mEq per liter Although the intravenous administration of procaine amide restored sinus rhythm on several occasions, the tachycardia recurred after weeks or days despite various prophylactic medication. Eventually the ventricular tachycardia could not be controlled despite the use of lidocaine, procaine amide, quinidine, digitalis, diphenylhydantoin, and propranolol in maximal, tolerated dosage. Precordial DC electrical shock had to be administered numerous times. Finally pacing with a transvenous catheter pacemaker in the right ventricle at 115 per minute without concomitant medication was found to be effective. There was no control of the atria by retrograde conduction. Since ventricular tachycardia recurred whenever the pacemaker was turned off even when the patient was maintained on antiarrhythmic drugs a permanent, fixed-rate (96 per minute) transvenous pacemaker was implanted on Oct 26 1967 When her heart was paced at this lower rate the patient experienced repeated attacks of ventricular tachycardia even after quinidine had been added to the pacemaker therapy Quinidine was therefore discontinued and she was given 120 mg of propranolol daily together with digoxin to overcome any tendency of propranolol to cause heart failure. The arrhythmia was now controlled but

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Pacemaker rhythm had to be restored by DC shock after an increase in the pacing rate to 125 per minute failed to terminate the arrhythmia. It was hoped that more effective prophylaxis would be attained by permanent pacing at 104 per minute instead of 96 per minute since a relapse had occurred with the latter rate. However the more rapid pacing had to be abandoned because the patient could not tolerate the unpleasant palpitation. Therefore the pacing rate was diminished to 98 per minute, but the propranolol dosage was increased to 160 mg daily. Sodium restriction and intermittent diuretic therapy were added to the digoxin to avoid the precipitation of heart failure even in the absence of ventricular tachycardia, because of the increased dose of propranolol. On this medical regimen together with artificial cardiac pacing at 98 per minute she has now remained comfortable and active, free of arrhythmia and congestive heart failure for 14 months.

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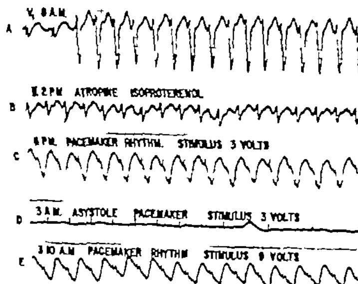


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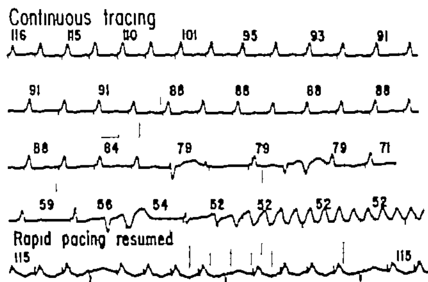


Fig. 2. Recurrent ventricular tachycardia-fibrillation suppressed by transvenous pacing at 118 per minute. Continuous tracing reveals appearance ventricular premature beats with slowing of pacemaker rate from 116 to 79 per minute. With further slowing to 52 per minute, ventricular tachycardia reappears.

time of pacemaker insertion the threshold stimulus was determined to be one volt and the pacing stimulus was set at 3 volts to allow a suitable safety factor. Stable pacemaker rhythm was maintained for 12 hours when the patient suddenly became asystolic despite continued pacemaker stimulation. After 10 minutes of resuscitative efforts, an increase in the pacing stimulus from 3 to 9 volts temporarily restored an effective cardiac contraction. However, the patient died shortly thereafter. The pacemaker unit and dry cell were examined and found to be functioning normally.

Patient 4. A 68-year-old man with mitral regurgitation experienced ventricular fibrillation, apparently due to quinidine toxicity. Despite drug therapy he required 20 DC shocks for recurrent ventricular tachycardia and fibrillation. His arrhythmias were suppressed first by a sinus tachycardia of 120 to 130 per minute induced by atropine and isoproterenol,[17] then by transvenous pacing at 118 per minute. Pacing enabled us to discontinue all drugs. Slowing of the pacing rate caused immediate reappearance of ventricular tachycardia (Fig. 2). Pacing at 115 was resumed for 4 days during which no ventricular premature systoles were observed on continuous monitoring. The patient was discharged after two weeks and has remained well.

Patient 5. Eight days after renal transplantation a 24-year-old woman suffering from systemic vasculitis required 35 DC shocks to abolish repeated ventricular tachycardia and fibrillation, apparently precipitated by drug-induced respiratory depression and unresponsive to lidocaine and procaine amide. Although a sinus tachycardia of 140 to 150 per minute induced by atropine and isoproterenol completely suppressed the arrhythmias for 2 hours and permitted pacemaker insertion under elective conditions, ventricular tachycardia and fibrillation later recurred while she was being paced at 120. The intravenous administration of lidocaine restored a stable pacemaker rhythm. After 40 hours it was possible to discontinue lidocaine and pacing. She had no recurrence of arrhythmias but succumbed to sepsis five weeks later.

Patient 6. A 48-year-old man with a previous myocardial infarction and ventricular aneurysm was admitted to the hospital for treatment of congestive heart failure. On the second day ventricular fibrillation developed, possibly due to digitalis intoxication (Fig. 3). Because lidocaine, procaine amide, and atropine failed to prevent 11 additional episodes of ventricular flutter and fibrillation, transvenous pacing was commenced at 120 per minute. However, this was also ineffective and was discontinued after 3 hours. One day later ventricular fibrillation recurred. After 6 episodes of this arrhythmia with a 45 minutes despite drug therapy pacing was reinstituted at 150 per minute in the belief that the previous pacing rate had been too slow to suppress the ventricular foci. However, despite the rapid pacing supplemented by procaine amide, propranolol, and a levarterenol drip sufficient to maintain a systolic pressure of 80 mm. Hg the patient required 26 additional DC shocks in the next 4 hours. Pacing was then discontinued. Although ventricular premature systoles persisted for several days, no further antiarrhythmic drugs nor resuscitation were required. His congestive heart failure was managed without digitalis and he was discharged from the hospital two months later.

Patient 7. A 73-year-old man with hypertensive heart disease and congestive heart failure was admitted to the hospital because of digitalis intoxication manifested by multifocal ventricular premature systoles and paroxysms of ventricular tachycardia. Lidocaine administered intravenously was followed by sinus rhythm but with frequent periods of sinus arrest. Temporary transvenous ventricular pacing

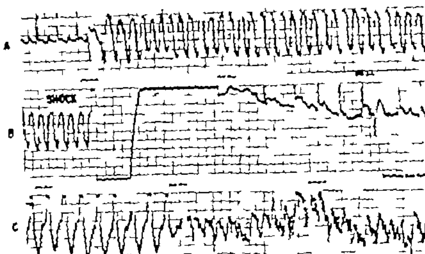


Fig. 3. Recurrent ventricular tachycardia-flutter-fibrillation probably due to digitalis. *A*, Ventricular tachycardia-flutter. *B*, Termination of VT by electric shock. *C*, Pacemaker rhythm with temporary complete capture at 150 per minute followed by ventricular fibrillation. Pacing was discontinued and there were no further attacks.

was instituted to suppress the ventricular arrhythmias and permit continued administration of antiarrhythmic drugs without risk of asystole due to further depression of the sinus node. Frequent ventricular premature systoles occurred during pacing at 95 per minute but these disappeared after the addition of procaine amide 500 mg every 4 hours. When pacing and procaine amide were discontinued 48 hours later, his electrocardiogram disclosed normal sinus rhythm. He had no further arrhythmias and was discharged.

Discussion

Cardiac pacemakers have been employed extensively not only to avoid ventricular asystole but also to prevent recurrent ventricular tachycardia and fibrillation in patients with complete heart block and with sinus bradycardia. In the 7 patients whose case histories we have reported, we have employed transvenous cardiac pacemakers to suppress frequently recurring ventricular tachycardia-fibrillation in patients without heart block and with normal heart rates between attacks. When cardiac pacemakers are inserted in patients with advanced heart block or bradycardia, pacing the heart at rates of 60 to 80 per minute usually prevents the recurrence of the tachyarrhythmia. Presumably these rates suffice to prevent "escape" tachyarrhythmias which occur when the basic rate is less than 50 per minute. However, when the patient's basic cardiac rate is in the range of 60 to 100 per minute between attacks the heart must be paced at rates of 110 to 120 or higher ("overdriving") to suppress recurrent ventricular tachycardia.

The mechanism responsible for ventricular arrhythmias in patients with slow heart rates is uncertain. Prolongation of diastole may permit diastolic depolarization of ectopic pacemaker cells to continue until they attain the threshold potential and fire ventricular systoles. But other factors must account for an increase in the automaticity of the latent pacemaker to explain the tachyarrhythmia. Slowing of the heart may cause a sufficient delay in repolarization of a group of cells to allow them to re-excite adjacent cells which had repolarized earlier and were again excitable.[11] Such asynchrony of recovery of excitability has long been invoked as an important factor in producing ectopic tachyarrhythmias. Han and associates have reported observations indicating that such temporal dispersion of recovery of excitability was a function of heart rate. At lower basic frequency of heart rate there was a greater range of duration of refractory periods and action potential than at higher rates.

Local potential differences may also be

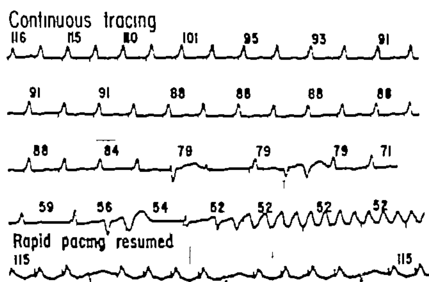


Fig 2 Recurrent ventricular tachycardia fibrillation suppressed by transvenous pacing at 118 per minute. Continuous tracing reveals appearance ventricular premature beats with slowing of pacemaker rate from 116 to 79 per minute. With further slowing to 52 per minute ventricular tachycardia reappears.

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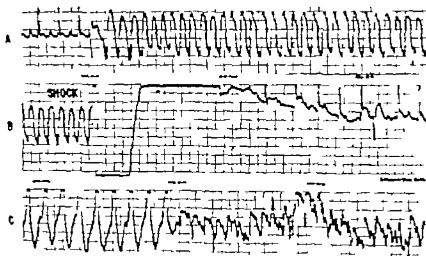


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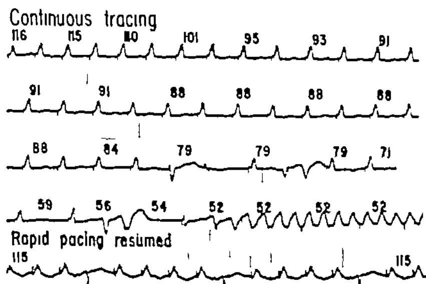


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The effect of diphenylhydantoin on atrioventricular and intraventricular conduction in man

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Walter D. Berkowitz, M.D.†
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Diphenylhydantoin (DPH) has been shown to be an effective agent in the treatment of ventricular arrhythmias associated with a variety of clinical causes.[1-7] Experimentally, DPH has been demonstrated to be especially effective in counteracting the electrophysiological manifestations of digitalis toxicity.[8] In a recent clinical study, DPH was reported to shorten the P-R interval over a range of controlled heart rates.

It was the purpose of this study to more precisely define the effects of DPH on atrioventricular and intraventricular conduction using the technique of His bundle recordings.

Methods

Right heart catheterization was performed in the nonsedated state on a total of 13 patients. All subjects were advised of the nature of the study and a signed consent obtained. Three patients were normal volunteers and the remaining 10 patients had arteriosclerotic heart disease, all of whom were taking maintenance digitalis. The indications for treatment with DPH in the 10 patients were frequent premature ventricular contractions of unifocal or multifocal origin (9 patients) and atrial tachycardia with A-V block (1 patient). DPH was administered intravenously at a rate of 25 to 50 mg. per minute until either the arrhythmia was abolished or a maximum dose of 1,000 mg. was given. In no case was it necessary to terminate treatment because of side effects. Constant electrocardiographic monitoring was maintained throughout the procedure. A tripolar electrode catheter was percutaneously introduced into the right femoral vein and fluoroscopically positioned at the tricuspid valve. The proximal electrode terminals were led into the AC input of an ECG preamplifier using a distribution switch box† which permitted the selection of multiple bipolar leads (Leads I and II, II and III, I and III). The filter frequencies of the ECG preamplifier were set at 40 to 500 c.p.s. His bundle electrograms were recorded simultaneously with a standard lead electrocardiogram. An additional bipolar electrode catheter was percutaneously introduced into an antecubital vein and

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toxicity was an important causative factor Previous reports usually of solitary cases suggested that the tachyarrhythmia was consistently suppressed when the pacing rate exceeded 110 per minute whereas lower rates were often ineffective In our experience pacing was effective in 4 of the 7 patients and was ineffective in 2 patients with maximal pacing of 120 per minute and in one who was paced at 150 per minute One of the latter three recovered spontaneously after ineffective pacing was discontinued Temporary control was obtained in some cases by inducing sinus tachycardia with intravenous atropine and isoproterenol until a pacemaker could be inserted The antiarrhythmic effect of rapid pacing may be due to shortening of diastole and abbreviation of repolarization thus inhibiting asynchronous areas of repolarization with local potential differences. In this series of patients there is one in whom previously refractory ventricular tachycardia has been suppressed for 14 months by means of rapid pacing with a permanently implanted pacemaker and a combination of propranolol and digoxin

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Table II *Effects of DPH on A V and I V conduction (msec.)*

Patient	Heart rate						
	80	*90*	*100*	*110*	*120*	*130*	*140*
1 P H	149	170	183	—	283	—	—
P H(D)*	108	136	163	—	224	—	—
H-Q	48	48	48	48	48	—	—
H-Q(D)	48	48	48	48	48	—	—
2 P H	180	204	240	W†	—	—	—
P H(D)	138	180	210	258	—	—	—
H-Q	54	54	54	54	54	—	—
H-Q(D)	54	54	54	54	54	—	—
3 P H	123	—	143	170	—	208	—
P H(D)	118	—	135	160	—	196	—
H-Q	42	—	42	42	—	42	—
H-Q(D)	42	—	42	42	—	42	—
4 P H	130	—	198	—	227	276	296
P H(D)	117	—	136	—	161	167	186
H-Q	37	—	37	—	37	37	37
H-Q(D)	37	—	37	—	37	37	37
5 P-H	88	—	—	—	—	—	—
P H(D)	88	—	—	—	—	—	—
H-Q	67	—	—	—	—	—	—
H-Q(D)	67	—	—	—	—	—	—
6 P H	396	435	468	—	—	—	—
P H(D)	382	409	442	475	—	—	—
H-Q	59	59	59	59	—	—	—
H-Q(D)	59	59	59	59	—	—	—
7 P H	—	98	113	127	145	—	165
P H(D)	—	100	110	125	140	—	158
H-Q	—	48	48	48	48	—	48
H-Q(D)	—	48	48	48	48	—	48
8 P-H	—	112	145	171	198	—	211
P H(D)	—	79	105	125	158	—	165
H-Q	—	60	60	60	60	—	60
H-Q(D)	—	60	60	60	60	—	60
9 P-H	79	118	—	138	—	—	—
P-H(D)	79	118	—	132	—	—	—
H-Q	60	60	—	60	—	—	—
H-Q(D)	60	60	—	60	—	—	—
10 P H	—	229	—	248	279	W	—
P H(D)	—	210	—	217	260	260	—
H-Q	—	55	—	55	33	55	—
H-Q(D)	—	55	—	55	55	55	—
11 P-H	96	—	119	—	189	—	—
P H(D)	91	—	112	—	189	—	—
H-Q	54	—	54	—	54	—	—
H-Q(D)	54	—	54	—	54	—	—
12 P H	—	—	112		Increasing A V block		—
P-H(D)	—	—	112	—	—	132	—
H-Q	—	—	43	—	—	43	—
H-Q(D)	—	—	43	—	—	43	—
13 P H	} Atrial fibrillation						
P-H(D)							
H-Q	39		—	—	—	—	—
H-Q(D)	39	—	—	—	—	—	—

*(D), Following DPH treatment.
†W, Wenckebach phenomenon.

Table I Clinical data

Patient	Age	Diagnosis	ECG	Dose of DPH (mg.)
1 P P	32	N	RBBB	250
2 W K	38	N	N	250
3 D K.	37	N	N	250
4 R V	69	ASHD CHF	Ventricular bigeminy	750
5 D J	52	ASHD Ventricular aneurysm	Old myocardial infarction PVC's	375
6 J H	69	ASHD	1 heart block PVC's	250
7 R G	56	ASHD	LAD LVH Ventricular bigeminy	500
8 E. K	58	ASHD Essential hypertension	LBBB Frequent PVC's	250
9 G L.	62	ASHD Pulmonary infarct	RBBB Ventricular bigeminy	500
10 G T	62	ASHD	1 heart block Frequent PVC's	250
11 J Mc	61	ASHD Chronic obstructive lung disease	LBBB Ventricular tachycardia	250
12 J S.	60	ASHD Stokes-Adams Digitalis toxicity	2 1 A V block	250
13 J H	70	ASHD CHF	Atrial fibrillation Multiple PVC's	250

Abbreviations N Normal; CHF congestive heart failure ASHD arteriosclerotic heart disease; RBBB, right bundle branch block; LBBB, left bundle branch block; PVC, premature ventricular contraction.

fluoroscopically positioned against the lateral wall of the right atrium at the junction of the superior vena cava This catheter was used to pace the right atrium at rates up to 140 per minute using a battery powered pacemaker* All records were made on an oscilloscopic photographic recorder† at paper speeds of 100 to 200 mm per second Measurements *(in milliseconds)* were made of the interval between the P wave or pacer spike to the His deflection (i e the P H interval) between the His deflection to the onset of the Q wave complex (i e. the H-Q interval) and between the His deflection and the terminal portion of the S wave of the QRS complex. The P H interval *is a* measure of atrioventricular conduction while the H-Q and H-S intervals are a measure of intraventricular conduction In the interest of brevity only the P H and H Q intervals are reported

*Medtronic, Inc., Minneapolis, Minn.
†Electronics for Medicine, White Plains, N Y

All equipment was grounded to insure against random currents.

Results

Table I lists the essential clinical data on the 13 patients treated in this study The dose of DPH ranged between 250 and 750 mg Except for yawning and somnolence *(Patients 4 and 6) no* serious side effects were noted In all cases DPH was effective in either abolishing or significantly lowering the number of premature ventricular contractions.

The effects of DPH on atrioventricular and intraventricular conduction over a range of paced heart rates are presented in Table II The duration of the P wave did not change throughout the pacing procedures. In the three normal subjects (Patients 1 2 and 3) DPH caused a shortening of the P H interval at all heart rates tested The H-Q intervals remained constant as did the H-S intervals which

Table II Effects of DPH on A V and I V conduction (msec.)

Patient	Heart rate						
	80	90	100	110	120	130	140
1 P H	149	170	183	—	285	—	—
P-H(D)*	108	136	163	—	224	—	—
H-Q	48	48	48	48	48	—	—
H-Q(D)	48	48	48	48	48	—	—
2 P H	180	204	240	W†	—	—	—
P H(D)	138	180	210	258	—	—	—
H-Q	54	54	54	54	54	—	—
H-Q(D)	54	54	54	54	54	—	—
3 P H	123	—	143	170	—	208	—
P H(D)	118	—	135	160	—	196	—
H-Q	42	—	42	42	—	42	—
H-Q(D)	42	—	42	42	—	42	—
4 P H	130	—	198	—	227	276	296
P H(D)	117	—	136	—	161	167	186
H-Q	37	—	37	—	37	37	37
H-Q(D)	37	—	57	—	37	37	37
5 P H	88	—	—	—	—	—	—
P-H(D)	88	—	—	—	—	—	—
H-Q	67	—	—	—	—	—	—
H-Q(D)	67	—	—	—	—	—	—
6 P H	396	435	468	—	—	—	—
P H(D)	382	409	442	475	—	—	—
H-Q	59	59	59	59	—	—	—
H-Q(D)	59	59	59	59	—	—	—
7 P-H	—	98	113	127	145	—	165
P H(D)	—	100	110	125	140	—	158
H-Q	—	48	48	48	45	—	48
H-Q(D)	—	48	48	48	48	—	48
8 P H	—	112	145	171	198	—	211
P H(D)	—	79	105	125	158	—	165
H-Q	—	60	60	60	60	—	60
H-Q(D)	—	60	60	60	60	—	60
9 P H	79	118	—	138	—	—	—
P H(D)	79	118	—	132	—	—	—
H-Q	60	60	—	60	—	—	—
H-Q(D)	60	60	—	60	—	—	—
10 P H	—	229	—	248	279	W	—
P-H(D)	—	210	—	217	260	260	—
H-Q	—	55	—	55	55	55	—
H-Q(D)	—	55	—	55	55	55	—
11 P H	96	—	119	—	189	—	—
P H(D)	91	—	112	—	189	—	—
H-Q	54	—	54	—	54	—	—
H-Q(D)	54	—	54	—	54	—	—
12 P H	—	—	112		Increasing A-V block		—
P H(D)	—	—	112	—	—	132	—
H-Q	—	—	43	—	—	43	—
H-Q(D)	—	—	43	—	—	43	—
13 P-H	*Atrial fibrillation*						
P H(D)	*Atrial fibrillation*						
H-Q	39		—	—	—	—	—
H-Q(D)	39	—	—	—	—	—	—

*(D), Following DPH treatment.
†W Wenckebach phenomenon.

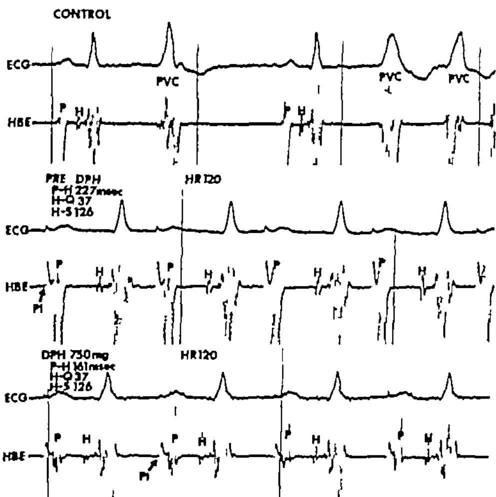


Fig 1 The top tracing in each panel is the standard electrocardiographic lead (*ECG*) and the bottom tracing is the His bundle electrogram (*HBE*). The top panel illustrates multiple premature ventricular contractions (*PVC's*). Prior to DPH treatment (middle panel) the atrium was paced at a rate of 120 per minute during which time the P H interval measured 227 msec. The H-Q and H S intervals measured 37 and 126 msec, respectively. In the bottom panel the P H interval measures 161 msec at the same paced atrial rate of 120 per minute following the administration of 750 mg DPH. The H-Q and H-S interval remained constant. *PI* Pacer impulse.

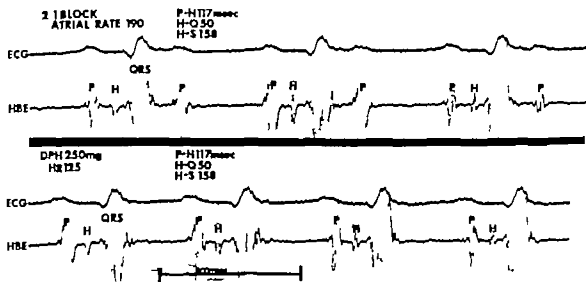


Fig 2 The top panel illustrates 2 1 A V block in a patient suspected of digitalis toxicity. The nonconducted P waves are blocked *proximal to* the His bundle. Following 250 mg of DPH (bottom panel) the atrial rate is decreased to 125 per minute and there is 1 1 A V conduction. DPH did not effect the P H H-Q, or H S intervals.

are not listed In four patients (Patients 4 6 8 and 10) treated for ventricular arrhythmias, DPH produced a shortening of the P H interval at all paced heart rates. DPH did not alter the H-Q intervals. A representative example of these findings is illustrated in Fig 1 The middle panel was taken prior to treatment with DPH at a paced atrial rate of 120 per minute. At this heart rate the P H interval was 227 msec This panel also demonstrates the ability of supraventricular pacing to control ventricular arrhythmias. Following 750 mg of DPH (bottom panel) the P H interval at the same paced atrial rate was 161 msec. and the H-Q interval remained constant.

In three patients (7 9 and 11) DPH produced no appreciable change in the P H interval at various heart rates. In no case was the P H interval prolonged and in no case was intraventricular conduction time altered.

I the one case of atrial fibrillation treated for premature ventricular contractions, DPH did not affect the H-Q interval. Patient No 12 presented with digitalis toxicity and 2 1 A V block. DPH (250 mg) restored 1 1 conduction at a slower atrial rate (Fig 2)

Discussion

The results of the present study are in agreement with a previous report from this laboratory in which the effects of DPH on the total P R interval was evaluated. As demonstrated in the present study the shortening of the P H interval following DPH reflected the enhancement of A V conduction The results of the present study are also in agreement with experimental animal findings in which DPH had little or no effect on intraventricular conduction as determined by the H-Q or H S intervals.[23]

The effects of DPH on atrioventricular and intraventricular conduction differ from those of other antiarrhythmic agents such as procaine amide and propranolol. In man therapeutic doses of propranolol (0 1 mg per kilogram of body weight) cause a prolongation of the P H interval at any given heart rate, and do not alter the H-Q or H S intervals.[14] Preliminary observations in man indicate that the well known effect of procaine amide to prolong the P R interval is predominantly the result of a prolongation in the H-Q interval.[4] In addition, procaine amide can cause a prolongation in the H S interval Thus, procaine amide prolongs conduction along the His-Purkinje system (increase in H-Q and H S intervals) while DPH enhances A V conduction (P H interval) and has little or no effect on intraventricular conduction. It has been previously demonstrated and was true of the results of the present study that the duration of the P wave (as determined by intra-atrial electrograms and standard lead electrocardiograms) does *not* change throughout right atrial pacing procedure.[23] Thus, the enhancement of A V conduction (i.e. shorter P H interval) is probably the result of DPH's effect on A V nodal transmission time Straus and associates[9] have reported that in the isolated atrial preparation DPH improves conduction The effects of DPH on the action potential of A V nodal cells has not been reported.

The mechanism of action whereby DPH causes an enhancement of A V conduction is not known. It would appear that it is neither anticholinergic nor sympathomimetic since the sinus rate following DPH was not significantly different from control values. In digitalis toxicity DPH is known to cause a reversal of the potassium efflux produced by the glycoside.[17] It is perhaps this reversal of ion flux which accounts for the enhanced A V conduction.

The electrophysiological manifestations of digitalis toxicity are (1) enhanced ventricular automaticity (2) prolongation of A V conduction (3) prolongation of I V conduction (in animals at very high digitalis doses) and (4) suppression of sinus rate. DPH has been demonstrated to antagonize these toxic manifestations of digitalis.[4,23] It has been suggested that alterations in conduction are important determinants in the production of "re-entrant" type arrhythmias. Thus it would appear that DPH's lack of prolongation of I V conduction would lessen the likelihood of producing re-entrant arrhythmias.

Summary

The effects of DPH on atrioventricular and intraventricular conduction were stud

ied in 13 patients using an electrode catheter technique for recording His bundle activity DPH was found to enhance A V conduction (i e shorten the P H interval) over various paced heart rates. DPH did not prolong I V conduction as measured by the H-Q interval

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Experimental and laboratory reports

Digitalis toxicity and hypomagnesemia

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In a prior study we observed that serum magnesium levels were significantly lower in 13 digitalized patients with congestive heart failure (1.40 mEq. per liter [mEq./L.]) than in 72 control subjects (1.93 mEq./L.). Jackson and Meier[4] noted an excessive prevalence of hypomagnesemia in patients on diuretic drugs. We found frank hypomagnesemia in four patients with digitalis toxicity. These observations, coupled with the fact that magnesium deficiency leads to an intracellular deficit of potassium, suggested that hypomagnesemia contributes to the development of digitalis toxicity.

While some investigators have shown that the induction of hypomagnesemia (by feeding growing puppies a diet deficient in magnesium) facilitates the development of digitalis toxicity, others were unable to confirm this finding. Kleiger and associates observed that the arrhythmia produced by acetylstrophanthidin persisted longer in hypomagnesemic than in normal dogs. Kim and co-workers[3] observed a small but significant rise in serum magnesium concentration in patients subsequent to the dissipation of digitoxic arrhythmias. In most studies utilizing parenteral magnesium salts in the treatment of digitalis toxicity they were given empirically without determining plasma magnesium concentrations.[9,14] The resultant transient antiarrhythmic activity of magnesium salts may be analogous to the administration of potassium to normokalemic patients with digitalis toxicity. In these instances, potassium salts often have limited usefulness and may further depress atrioventricular conduction. In contrast, potassium salts are particularly effective when digitalis toxicity is associated with hypokalemia.

The purpose of this investigation was twofold: (1) to determine whether hypomagnesemia facilitates the development of digitalis toxicity and (2) to determine the

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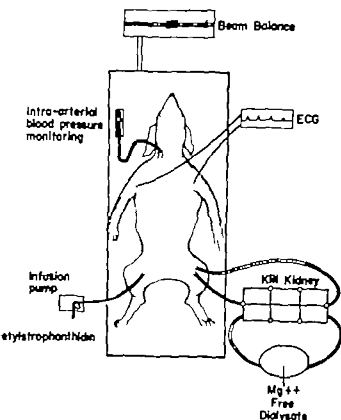


Fig. 1. Schematic drawing of animal experiment.

efficacy of intravenously administered magnesium sulfate in the treatment of digitalis toxicity associated with hypomagnesemia.

Methods and materials

Studies were performed in 19 adult mongrel dogs whose average weight was 20 kilograms. Anesthesia was induced by 25 mg. per kilogram of intravenous Pentothal Sodium and additional doses were given as needed to maintain anesthesia. The dogs were ventilated through a cuffed endotracheal tube with a Harvard respirator whose tidal volume and rate were adjusted to dog weight. The dogs were hydrated with 300 c.c. of isotonic saline. A two-layer Kiil kidney hemodialysis primed with 300 c.c. of normal saline was started using femoral arterial and venous cannulations. Magnesium-free deionized water was used for the dialysate bath. The following substances were added to 100 liters of deionized water: NaCl 620 Gm., $NaHCO_3$ 300 Gm., KCl 30 Gm., $MgCl_2$ 12 Gm., $CaCl_2$ 22 Gm., lactic acid 40 c.c., and glucose 100 Gm. This resulted in cation concentrations which approximated the ionized fraction found in normal canine plasma: Na 141 mEq./L., K 4.0 mEq./L., Mg 1.3 mEq./L., Ca 3.0 mEq./L., Cl 116 mEq./L., and HCO_3 35 mEq./L. During dialysis the dog's weight was continuously monitored on a beam balance and isotonic saline replacement was given in order to maintain a constant weight. Continuous intraarterial blood pressure was determined with a strain-gauge transducer and monitored on an oscilloscope. Serial Lead II electrocardiograms were obtained with a direct-writing electrocardiograph (Fig. 1).

Acetyl strophanthidin was infused through an indwelling venous catheter at a rate of 100 μg per minute by means of a constant infusion pump. The infusion was continued until the onset of digitalis toxicity as evidenced by A-V dissociation, nodal tachycardia, or ventricular tachycardia.

All dogs were dialyzed with a normal bath as well as a bath identical in composition but free of magnesium. Three groups of animals were studied (Fig. 2).

Group I. Eight dogs had infusions of acetyl strophanthidin after ½, 3½, and 6½ hours of dialysis with a normal bath. The fourth acetyl strophanthidin infusion was performed after 3 additional hours of dialysis utilizing the magnesium-free dialysate.

Group II. Eight dogs had infusions of acetyl strophanthidin after ½ and 3½ hours of dialysis with a normal bath. The third and fourth acetyl strophanthidin infusions were performed after 3 and 6 additional hours of dialysis with the magnesium-free dialysate.

Group III. In order to assure that there was no cumulative effect due to repeated digitalization, the experiment was reversed. Three dogs had acetyl strophanthidin infusions performed at ½, 3½, and 6½ hours of dialysis with a magnesium-free bath. Then 4 c.c. of a 25 per cent magnesium sulfate solution was injected intravenously to correct the hypomagnesemia and terminate the arrhythmia. The fourth acetyl strophanthidin infusion was performed after 3 additional hours of dialysis with a normal bath.

In order to determine the efficacy of magnesium sulfate in the treatment of

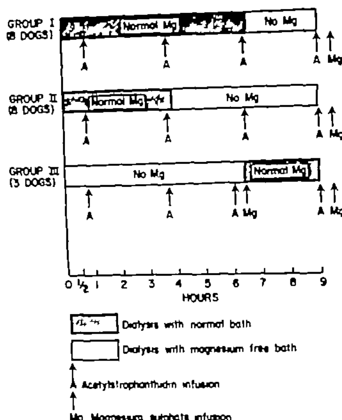


Fig. 2. Schematic representation of experimental models.

hypomagnesemic digitalis toxicity 2 to 7 c.c. of a 25 per cent magnesium sulfate solution was administered intravenously at a rate of approximately 1 c.c. per minute to several dogs in each group. Arterial blood samples, obtained during the control period prior to each infusion of acetyl strophanthidin and at the onset of digitalis toxicity were analyzed for sodium and potassium by flame photometry and for magnesium and calcium by atomic absorption spectroscopy. Serum magnesium levels were also determined after the administration of magnesium sulfate. Blood pH was measured at intervals with a Radiometer pH meter.

Results

Facilitation of digitalis toxicity by hypomagnesemia. In both groups (I and II) the first infusion required 30 per cent more acetyl strophanthidin to produce a toxic arrhythmia than did the second infusion because of an initial loading factor. In Group I the dose required to produce digitalis toxicity during the second and third infusion did not vary significantly. This indicates that after the first infusion there was no statistically significant cumulative or carry-over effect from the second to the third infusion of acetyl strophanthidin in the presence of constant serum magnesium levels. (See statistical appendix A.)

When serum magnesium levels were lowered by dialysis there was a statistically significant decrease in the amount of acetyl strophanthidin needed to produce an arrhythmia ($p < 0.05$). (See statistical appendix B.) An analysis of covariance indicated that the decrease in acetyl strophanthidin tolerance was directly related to the decrease in serum magnesium levels ($p < 0.05$). (See statistical appendix C.)

Hypomagnesemia was induced in a total of 19 dogs—8 in Group I, 8 in Group II

Table I Serum magnesium and amount of acetyl strophanthidin needed to produce digitalis toxicity in Group I

Group I Dog No.	Normal Mg bath						Low Mg bath	
	C_1* (mEq./L.)	A_1† (µg/Kg.)	C_2* (mEq./L.)	A_2† (µg/Kg.)	C_3* (mEq./L.)	A_3† (µg/Kg.)	C_4* (mEq./L.)	A_4† (µg/Kg.)
11	1.54	64.3	1.57	41.8	1.61	42.8	1.27	33.7
13	1.35	44.5	1.56	33.0	1.58	35.7	0.92	26.1
14	1.35	69.3	1.36	36.2	1.53	36.2	0.85	33.1
15	1.50	35.9	1.64	26.9	1.75	35.9	1.25	33.1
16	1.56	33.8	1.80	30.0	1.85	43.8	1.23	20.0
19	1.70	55.0	1.85	18.5	1.93	35.7	1.19	21.1
20	1.74	50.2	2.01	34.3	1.87	41.7	1.12	17.8
21	1.40	51.5	1.50	36.8	1.49	40.4	0.85	29.4
Mean	1.52	50.5	1.67	34.7	1.70	39.0	1.09	23.6

*C_1, C_2, C_3, C_4 = Serum Mg (mEq./L.) before first, second, third, and fourth infusions of acetyl strophanthidin.
†A_1, A_2, A_3, A_4 = Amount of acetyl strophanthidin (µg/Kg.) required to produce digitalis toxicity in the first, second, third, and fourth infusions.

Table II Serum magnesium and amount of acetyl strophanthidin needed to produce digitalis toxicity in Group II

Group II Dog No.	Normal Mg bath				Low Mg bath			
	C_1* (mEq./L.)	A_1† (µg/Kg.)	C_2* (mEq./L.)	A_2† (µg/Kg.)	C_3* (mEq./L.)	A_3† (µg/Kg.)	C_4* (mEq./L.)	A_4† (µg/Kg.)
2	2.15	72.1	2.22	61.8	1.63	33.5		
4	2.01	70.6	1.73	59.3	0.91	57.9	0.79	57.9
5	1.50	49.2	1.67	44.8	1.13	32.0	0.99	30.3
22	1.59	84.6	1.66	55.1	0.85	50.0	0.84	37.2
23	1.03	47.9	1.15	45.0	0.68	43.2	0.45	24.5
24	1.02	39.1	1.00	38.5	0.53	30.2	0.44	37.1
26	1.61	34.5	1.69	34.5	0.94	21.9	0.90	24.3
27	2.08	57.7	2.34	44.0	1.09	27.5	0.86	33.0
Mean	1.62	59.5	1.68	47.9	0.97	37.0	0.75	34.9

*C_1, C_2, C_3, C_4 = Serum Mg (mEq./L.) before first, second, third, and fourth infusions of acetyl strophanthidin.
†A_1, A_2, A_3, A_4 = Amount of acetyl strophanthidin (µg/Kg.) required to produce digitalis toxicity in the first, second, third, and fourth infusions.

and 3 in Group III (Tables I, II, and III). Excluding data from the first infusion, the reduction (44 per cent) of serum magnesium levels from 1.67 to 0.93 mEq./L. resulted in a 26 per cent reduction in the toxic dose of acetyl strophanthidin from 42.4 to 31.4 µg per kilogram.

Efficacy of magnesium sulfate in the treatment of digitalis toxicity associated with hypomagnesemia. Intravenous magnesium sulfate was administered to 17 dogs (8 in Group I, 6 in Group II, and 3 in Group III) in an attempt to correct the toxic arrhythmia associated with hypomagnesemia (Table IV). Restitution of sinus rhythm was observed in 13 dogs (76 per cent) almost immediately after intravenous administration of from 2 to 7 c.c. of a 25 per cent

Table III. Serum magnesium and amount of acetyl strophanthidin needed to produce digitalis toxicity in Group III

Group III Dog No.	Low Mg bath						Normal Mg bath	
	C_1 (mEq./L.)*	A_1† (µg/Kg.)	C_2 (mEq./L.)*	A_2† (µg/Kg.)	C_3 (mEq./L.)*	A_3† (µg/Kg.)	C (mEq./L.)*	A† (µg/Kg.)
17	1.11	45.9	0.94	34.4	0.70	46.7	1.53	37.9
18	1.45	46.7	1.12	44.4	0.82	42.7	1.47	36.2
28	1.33	60.2	0.81	26.6	0.65	35.0	1.72	35.9
Mean	1.30	50.9	0.96	35.1	0.72	41.5	1.57	36.7

*C_1, C_2, C_3, C_4. Serum Mg (mEq./L.) before first, second, third, and fourth infusions of acetyl strophanthidin.
†A_1, A_2, A_3, A_4. Amount of acetyl strophanthidin (µg/Kg.) required to produce digitalis toxicity in the first, second, third, and fourth infusions.

magnesium sulfate solution (Figs. 3 and 4). Magnesium sulfate failed to correct the arrhythmia in four dogs (Nos. 14, 15, 26, and 27). In two (Nos. 14 and 15) of this latter group, hypomagnesemia had not reduced the amount of digitalis necessary to induce digitalis toxicity (Table I).

Duration of arrhythmia associated with hypomagnesemia as compared to those associated with normal magnesium levels. In Group II, the duration of the hypomagnesemia-facilitated arrhythmia following the third infusion of acetyl strophanthidin (DT_3, Table IV) was not significantly longer than the arrhythmia induced after the second acetyl strophanthidin infusion (DT_2, Table IV) in the presence of normal magnesium levels. In the 13 experiments in which magnesium sulfate abolished the arrhythmia, it is notable that reversion of the arrhythmia was effected within minutes and frequently within seconds of the drug administration. In these instances the duration of the arrhythmia was much shorter than when not treated with magnesium sulfate.

Absence of cumulative effect of acetyl strophanthidin. In Group I, the dose of acetyl strophanthidin needed to produce digitalis toxicity was the same in the second as in the third infusion, demonstrating that under the conditions of this experiment there was no cumulative or carry-over effect of the acetyl strophanthidin.

The experiment was reversed in Group III (Table III) so as to determine whether the reduced dosage needed to produce digitalis toxicity during the fourth infusion of acetyl strophanthidin was due to accumulation of acetyl strophanthidin. Here, three dogs were initially dialyzed against a magnesium-free bath for six hours. Then 4 c.c. of a 25 per cent magnesium sulfate solution were infused and the dogs were dialyzed for an additional 3 hours with a normal magnesium bath. The amount of digitalis required during the fourth infusion of acetyl strophanthidin (with normal magnesium levels) was equal to or greater than the amounts required for the second and third (hypomagnesemic) infusions. This confirmed the fact that the reduction in the amount of acetyl strophanthidin needed to produce digitalis toxicity during all other experiments was due to hypomagnesemia rather than to the cumulative effect of acetyl strophanthidin. In Group III, prompt abolition of the arrhythmia associated with hypomagnesemia (third acetyl strophanthidin infusion) was accomplished by the administration of 4 c.c. of 25 per cent magnesium sulfate, whereas magnesium salts were ineffective in correcting the digitalis toxicity associated with normomagnesemia (fourth acetyl strophanthidin infusion).

Serum cation concentrations and pH. In 19 dogs (Groups I, II, and III) dialysis with a magnesium-free bath reduced serum magnesium levels from an average of 1.67 mEq./L. to 0.93 mEq./L., a decrease of 44 per cent. Potassium levels were un

Table I Serum magnesium and amount of acetyl strophanthidin needed to produce digitalis toxicity in Group I

Group I Dog No	Normal Mg bath						Low Mg bath	
	C_1 (mEq./L.)	A_1† (µg/Kg)	C_2 (mEq./L.)	A_2† (µg/Kg)	C_3 (mEq./L.)	A_3† (µg/Kg)	C_4 (mEq./L.)	A_4† (µg/Kg)
11	1 54	64 3	1 57	41 8	1 61	42 8	1 27	33 7
13	1 35	44 5	1 56	33 0	1 58	35 7	0 92	26 1
14	1 35	69 3	1 36	36 2	1 53	36 2	0 85	38.1
15	1 50	35 9	1 64	26 9	1 75	35 9	1 25	38 1
16	1 56	33 8	1 80	30 0	1 85	43 8	1 23	20 0
19	1 70	55 0	1 85	38 5	1 93	35 7	1 19	21 1
20	1 74	50 2	2 04	34 3	1 87	41 7	1 12	17 8
21	1 40	51 5	1 50	36 8	1 49	40 4	0 85	29 4
Mean	1 52	50 5	1 67	34 7	1 70	39 0	1 09	25 9

*C_1, C_2, C_3, C_4 = Serum Mg (mEq./L.) before first, second, third and fourth infusions of acetyl strophanthidin.
†A_1, A_2, A_3, A_4 = Amount of acetyl strophanthidin (µg/Kg) required to produce digitalis toxicity in the first, second, third, and fourth infusions

Table II Serum magnesium and amount of acetyl strophanthidin needed to produce digitalis toxicity in Group II

Group II Dog No	Normal Mg bath				Low Mg bath			
	C_1 (mEq./L.)	A† (µg/Kg)	C (mEq./L.)	A† (µg/Kg)	C_3 (mEq./L.)	A† (µg/Kg)	C (mEq./L.)	A† (µg/Kg)
2	2 15	72 1	2 22	61 8	1 63	33 5		
4	2 01	70 6	1 73	59 3	0 91	57 9	0 79	57 9
5	1 50	49 2	1 67	44 8	1 13	32 0	0 99	30 5
22	1 59	84 6	1 66	55 1	0 83	50 0	0 84	37 2
23	1 03	47 9	1 15	45 0	0 68	43 2	0 45	24 5
24	1 02	59 1	1 00	38 5	0 53	30 2	0 44	37 1
26	1 61	34 5	1 69	34 5	0 94	21 9	0 90	24 3
27	2 08	57 7	2 34	44 0	1 09	27 5	0 86	33 0
Mean	1 62	59 5	1 68	47 9	0 97	37 0	0 75	34 9

*C_1, C_2, C_3, C_4 = Serum Mg (mEq./L.) before first, second, third and fourth infusions of acetyl strophanthidin.
†A_1, A_2, A_3, A_4 = Amount of acetyl strophanthidin (µg/Kg) required to produce digitalis toxicity in the first, second, third, and fourth infusions.

and 3 in Group III (Tables I II and III) Excluding data from the first infusion the reduction (44 per cent) of serum magnesium levels from 1 67 to 0 93 mEq./L. resulted in a 26 per cent reduction in the toxic dose of acetyl strophanthidin from 42 4 to 31 4 µg per kilogram

Efficacy of magnesium sulfate in the treatment of digitalis toxicity associated with hypomagnesemia Intravenous magnesium sulfate was administered to 17 dogs (8 in Group I 6 in Group II and 3 in Group III) in an attempt to correct the toxic arrhythmia associated with hypomagnesemia (Table IV) Restitution of sinus rhythm was observed in 13 dogs (76 per cent) almost immediately after intravenous administration of from 2 to 7 c.c. of a 25 per cent

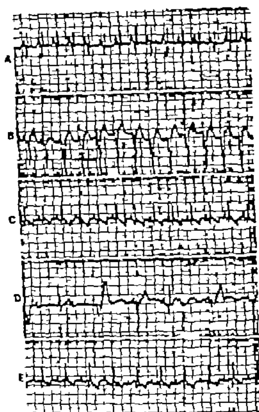


Fig. 3. After 3½ hours of dialysis with normal bath composition. *A*, Sinus rhythm before acetyl strophanthidin infusion. Serum magnesium 1.67 mEq./L. *B*, Digitalis toxicity after infusion of 1,137 µg. of acetyl strophanthidin (44.8 µg./Kg.). Serum magnesium 1.55 mEq./L.

After three hours of dialysis with magnesium-free bath. *C*, Sinus rhythm before acetyl strophanthidin infusion. Serum magnesium 0.99 mEq./L. Note S-T-segment depression and T-wave inversion. *D*, Digitalis toxicity after infusion of 825 µg. of acetyl strophanthidin (30.5 µg./Kg.). Serum magnesium 0.98 mEq./L. Hypomagnesemia facilitated the development of digitalis toxicity in that 27 per cent less acetyl strophanthidin was required than when the serum magnesium was 1.67 mEq./L. *E*, After 5 c.c. of 25 per cent $MgSO_4$ solution given intravenously over a 5 minute period. Serum magnesium 1.78 mEq./L. Note the rapid abolition of digitalis toxicity and restitution of sinus rhythm subsequent to the correction of hypomagnesemia.

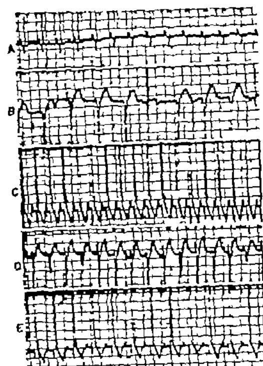


Fig. 4. After ½ hour of dialysis with normal bath composition. *A*, Sinus rhythm before acetyl strophanthidin infusion. Serum magnesium 1.56 mEq./L. *B*, A-V dissociation after infusion of 675 µg. acetyl strophanthidin (33.8 µg./Kg.). Serum magnesium 1.67 mEq./L.

After three hours of dialysis with magnesium-free bath. *C*, Sinus rhythm before acetyl strophanthidin infusion. Serum magnesium 1.23 mEq./L. Note S-T-segment depression and T-wave inversion. *D*, A-V dissociation after infusion of 400 µg. acetyl strophanthidin (20.0 µg./Kg.). Serum magnesium 1.2 mEq./L. Hypomagnesemia facilitated the development of digitalis toxicity in that 40 per cent less acetyl strophanthidin was required than when the serum magnesium was 1.56 mEq./L. *E*, Sinus rhythm returned immediately after 2 c.c. of 25 per cent $MgSO_4$ solution were administered intravenously over a two-minute period. Serum magnesium after a total of 5 c.c. of $MgSO_4$ = 4.3 mEq./L.

talis glycosides have dealt with potassium and calcium.[11-13] They have shown that digitalis protects against the toxic manifestations of potassium and conversely that the administration of potassium salts protects the myocardium against digitalis toxicity.[13] In addition, potassium depletion sensitizes the myocardium to the development of digitalis toxicity.[14] Other investigations have demonstrated that calcium affects myocardial contractibility and excitability and may occasionally potentiate the development of digitalis toxicity. Conversely, calcium chelating agents have been recom

Table IV

Dog No	*DT*	C_1	DT_2	C_2	DT_3	*C*	DT_4	*Mg*	*Response to 25 per cent MgSO and comment*
Group I									
11	15		13	1 61	13	1 27	2	2 4	*Sinus rhythm after 2 c.c. MgSO
13	13		11	1 58	18	0 92	3	6 87	*Sinus rhythm after 6 c.c. MgSO
14	20		13	1 53	15	0 85	10*	8 06	*9 c.c. $MgSO_4$ without conversion to sinus rhythm also no facilitation of digitalis toxicity by decreased magnesium
15	14		13	1 75	7	1 25	10	6 50	*Temporary sinus rhythm after 4 c.c. $MgSO_4$, then return of arrhythmia despite 14 c.c. MgSO also no facilitation of digitalis toxicity by decreased magnesium
16	18		54	1 85	2	1 23	7	4 3	Sinus rhythm after 5 c.c. MgSO
19	19		17	1 93	16	1 19	6	5 76	Sinus rhythm after 6 c.c. MgSO
20	5		27	1 87	25	1 12	9	5 38	Sinus rhythm after 7 c.c MgSO
21	20		12	1 49	25	0 85	7	4 3	*Sinus rhythm after 7 c.c MgSO
Group II									
2	15	2 22	14	1 63	ND		ND		
4	27	1 73	14	0 94	15	0 79	ND		
5	16	1 67	18	1 13	14	0 99	5	3 78	Sinus rhythm after 6 c.c. MgSO
22	7	1 66	7	0 85	16	0 84	6	5 71	*Sinus rhythm after 6 c.c. MgSO
23	12	1 15	22	0 68	12	0 45	3	1 97	Sinus rhythm after 2 c.c MgSO
24	8	1 00	19	0 53	23	0 44	3	4 89	*Sinus rhythm after 4 c.c. MgSO
26	16	1 69	22	0 94	18	0 90	20	8 27	13 c.c. MgSO without conversion to sinus rhythm
27	8	2 34	12	1 09	10	0 86	14	8 57	Temporary sinus rhythm after 6 c.c. $MgSO_4$ then return of arrhythmia despite 10 c.c MgSO
Group III									
17	10	0 94	10	0 7			9†	3 43	*Sinus rhythm immediately after 2 c.c. MgSO †Sinus rhythm after 6 c.c MgSO
18	11	1 12	28	0 82	4		10†	4 63	*Sinus rhythm immediately after 4 c.c. MgSO † Arrhythmia persisted despite 4 c.c. MgSO
28	16	0 81	10	0 65	5		3†	3 26	*Sinus rhythm after 4 c.c. MgSO †Sinus rhythm after 2 c.c. MgSO

DT DT_2, DT_3, and DT = Duration (min.) of first, second, third, and fourth arrhythmia.
C_2, C_3, and C_4 = Serum Mg (mEq./L.) before acetyl strophanthidin infusion.
Mg = Serum Mg after infusion of magnesium sulfate.
ND = Not determined.

changed No significant changes were noted in serum sodium or calcium levels during the experimental period The pH remained constant

Electrocardiographic changes A V dissociation nodal tachycardia or ventricular tachycardia were taken as the end point of digitalis toxicity For each individual animal the arrhythmias induced *during each* infusion of acetyl strophanthidin were of the same type Electrocardiographic changes associated with hypomagnesemia were primarily those of S-T-segment depression and T wave inversion Marked S-T-segment depression was seen in only a few experiments and did not correlate with the degree or duration of hypomagnesemia (Figs 3 and 4)

Discussion

Most studies relating electrolytes to the function and toxic manifestations of digi

mended for the treatment of digitalis toxicity, but their therapeutic benefits are often evanescent.[20,21]

The primary cardiovascular effects of magnesium involve myocardial conduction and contraction as well as blood pressure regulation. Some investigators feel that magnesium depresses conduction and the spontaneous rhythm of the heart. They suggest that one of the mechanisms underlying these effects may be decreased loss of intracellular potassium as a result of reduction in membrane permeability to potassium. It is postulated that magnesium activates membrane adenosine triphosphatase, an enzyme responsible for active transport of cations across the cell membrane.

Marked hypermagnesemia has dramatic cardiovascular effects which include vasodilatation, hypotension, and bradycardia; the effects of hypomagnesemia on the cardiovascular system are not clear.[17,18]

Chronic magnesium deficiency in animals causes inflammatory, degenerative, and fibrotic changes in the myocardium, but no specific functional changes have been observed.[20,21]

The current study demonstrates that Kiil kidney dialysis is a hemodynamically stable method of inducing acute hypomagnesemia while maintaining other serum cation concentrations constant. Serum magnesium levels were reduced 44 per cent after 3 to 6 hours of dialysis with a magnesium-free bath. The fact that this degree of hypomagnesemia reduces the toxic dose of acetyl strophanthidin by 26 per cent suggests that hypomagnesemia predisposes to the development of digitalis toxicity.

Several studies have shown that chronic magnesium deficiency results in a reduction in intracellular potassium.[4, 22-25] This has been attributed to the fact that magnesium deficiency leads to disturbed oxidative phosphorylation which is essential for the maintenance of normal intracellular potassium concentrations. The decreased tolerance to acetyl strophanthidin observed in this study may be directly related to hypomagnesemia or possibly mediated by a decreased intracellular potassium concentration. In therapeutic doses, digitalis blocks adenosine triphosphatase activity in the cell membrane and thus inhibits active transmembrane transport of potassium. This results in a decrease in the intracellular potassium concentration (Fig. 5). Magnesium is a metallocoenzym and activates adenosine triphosphatase. Hypomagnesemia may therefore contribute to digitalis adenosine triphosphatase blockade and result in a greater loss of intracellular potassium. These observations are of particular clinical significance in view of the fact that many diuretic drugs produce both hypokalemia and hypomagnesemia.

The electrocardiographic changes associated with hypomagnesemia alone were S-T-segment depression and T wave inversion. The S-T-segment depression was marked in some instances but did not correlate with the degree of hypomagnesemia. We did not observe peaking of the T wave in association with hypomagnesemia as described by other investigators.[24] This may be due to rapid induction of hypomagnesemia by dialysis as compared to its slower production by feeding a magnesium-deficient diet. The fact that the electrocardiographic changes of hypomagnesemia (S-T segment depression and T wave inversion) are similar to the changes of both hypokalemia and digitalis suggests that they have a common effect on myocardial repolarization.

The effects of magnesium salts in various arrhythmias, including those induced by digitalis, have been studied by several investigators.[7-18] It has been shown that the slow intravenous infusion of 20 c.c. of a 20 per cent magnesium sulfate solution has little effect on the normal electrocardiogram and carries little clinical risk. Intravenous magnesium sulfate has been used to treat paroxysmal atrial and ventricular tachycardia but atrial fibrillation is not usually affected. It has been used with limited success in digitalis toxicity but in these instances it was administered without determining serum magnesium levels.

In this study the intravenous infusion of 2 to 7 c.c. of a 25 per cent magnesium sulfate solution (1 c.c. per minute) abolished the toxic arrhythmia associated with hypomagnesemia in 13 of 17 animals (76 per cent). Its antiarrhythmic action was prompt and terminated the toxic arrhythmia permanently. As mentioned previously, magnesium sulfate was more effective in the treatment of digitalis toxicity

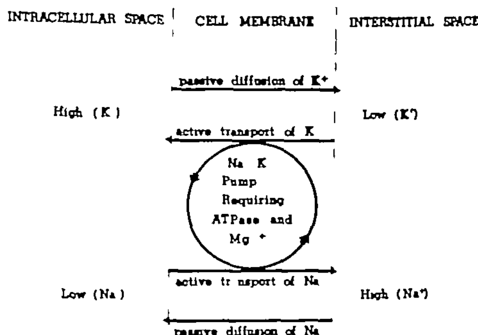


Fig 5 *A* Normal interrelationship of magnesium and digitalis with transmembrane electrolyte transport. The high intracellular concentration of K and the high extracellular concentration of Na results in passive diffusion of these ions away from these regions of high concentration. This is opposed by active transport of Na^+ and K by the Na K pump. This mechanism requires adenosine triphosphatase (ATPase) and its metallocoenzyme Mg^{++}. Normally a high intracellular concentration of K^+ is maintained as well as a low intracellular concentration of Na^+.

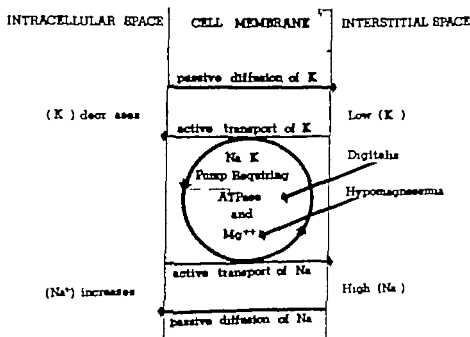


Fig 5 *B* An interrelationship of magnesium and digitalis with transmembrane electrolyte transport in which digitalis blocks ATPase, resulting in a reduction of active transport of K 1 to the cell while passive diffusion continues. This leads to a reduction in intracellular potassium. Hypomagnesemia also leads to a reductio in active transport of K^+ into *the cell resulting in a reduction in intracellular potassium.*

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Appendix tables

Table A. Sums of squares (toxicity)

Source of variation	*Degrees of freedom*	*Sums of squares*	*Mean square*
Between drugs	2	1010 6487	505 3244
Within drugs	27	2718 7580	100 6947
Total	29	3729 4067	

Table B

Dog K	I		II		III			
	C	*A*	C_1	*A*	C_4	*A*	*C*	*A*
4	1 73	50 3	0 94	57 9	0 79	57 9		
5	1 67	44 8	1 13	32 0	0 99	30 5		
23	1 66	53 1	0 85	50 0	0 84	37 2		
25	1 15	45 0	0 68	43 2	0 45	24 5		
24	1 00	38 5	0 53	30 2	0 44	37 1		
26	1 69	34 5	0 94	21 9	0 90	24 3		
27	2 34	44 0	1 09	27 5	0 86	33 0		
17	1 11	45 9	0 94	34 4	0 70	36 7		
18	1 43	46 7	1 12	44 4	0 82	32 7		
28	1 33	60 2	0 81	26 6	0 65	25 0	31 6	1181
Total	15 13	474 0	9 03	368 1	7 44	338 9	31 6	1181
Means	1 513	47 4	0 903	36 81	0 744	33 89	1 053	393 67

when the arrhythmia was associated with hypomagnesemia than when normal magnesium levels were present

Although the precise mechanism of its antiarrhythmic activity is not known it may be due to correction of the hypomagnesemia A second possibility supported by observations in our laboratory suggests that the administration of magnesium sulfate promotes the movement of potassium into the intracellular space This would antagonize the effect of digitalis on intracellular potassium A third possible explanation is that correction of the hypomagnesemia may decrease membrane permeability to calcium This would result in a decreased intracellular movement of calcium which would also reduce the effect of digitalis

Summary

Four patients with digitalis toxicity were found to be hypomagnesemic and normokalemic A significantly lower mean serum magnesium was noted in a group of digitalized heart failure patients (1 40 mEq/L) than in matched normal subjects (1 93 mEq/L) These observations coupled with the fact that both digitalis and magnesium deficiency lead to a decrease in intracellular potassium suggested that hypomagnesemia might contribute to the development of digitalis toxicity

To determine whether hypomagnesemia facilitates the development of digitalis toxicity serial acetyl strophanthidin infusions were performed in 19 adult mongrel dogs. Hypomagnesemia was achieved by Kiil kidney dialysis. While dialysate electrolyte concentration corresponded to normal canine plasma acetyl strophanthidin was infused (100 μg per minute) three times at three hour intervals Hypomagnesemia was then induced by three hours of magnesium free dialysis and acetyl strophanthidin was again infused

Mean serum magnesium was reduced 44 per cent (1 67 to 0 93 mEq./L) This was accompanied by a 26 per cent reduction in the amount of acetyl strophanthidin needed to produce a toxic arrhythmia (42 4 to 31 4 μg per kilogram) Restitution of sinus rhythm was observed in 13 dogs immediately after the intravenous infusion of 2 to 7 c.c. of 25 per cent magnesium sulfate

These studies have shown that hypomagnesemia facilitates digitalis toxicity which can be promptly terminated with magnesium sulfate Since diuretic drugs may produce hypomagnesemia as well as hypokalemia and both may predispose to digitalis toxicity it is suggested that serum magnesium as well as potassium levels be determined in patients with digitalis toxicity

The authors greatly acknowledge the technical assistance rendered by Roberto Gomez.

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Appendix tables

Table A. Sums of squares (toxicity)

Source of variation	Degrees of freedom	Sums of squares	Mean square
Between drugs	2	1010 6487	505 3244
Within drugs	27	2718 7580	100 6947
Total	29	3729 4067	

Table B

Dog No.	I		II		III			
	C	A	C	A	C	A	C	A
4	1 73	59 3	0 94	57 9	0 79	57 9		
5	1 67	41 8	1 13	32 0	0 99	30 5		
22	1 66	55 1	0 85	50 0	0 84	37 2		
23	1 15	45 0	0 68	43 2	0 43	24 5		
21	1 00	38 5	0 53	30 2	0 44	37 1		
26	1 49	34 5	0 94	21 9	0 90	24 3		
27	2 34	44 0	1 09	27 5	0 86	33 0		
17	1 11	45 9	0 94	34 4	0 70	36 7		
18	1 45	46 7	1 12	44 4	0 82	32 7		
38	1 33	60 2	0 81	26 6	0 65	25 0	31 6	1181
Total	15 13	471 0	9 03	368 1	7 44	338 9	31 6	1181
Means	1 513	47 4	0 903	36 81	0 744	33 89	1 053	393 67

Table C Analysis of covariance F test one way classification

	D.O F	ΣC^2	ΣCA	ΣA^2	Reduction	D O F	Deviation from regression sum of sq.	Mean square
Treatments	2	3 2958	57 7112	1010 6487				
Error	27	2 0469	4 2221	2718 7580	8 7088	26	2710 0492	104 233
T + E	29	5 3427	61 9333	3729 4067	717 9392	28	3011 4675	
						2	301 4183	150 709

Statistical appendix

A To test whether there was a cumulative or carry-over effect from the acetyl strophanthidin infusions in the presence of constant magnesium the data A_1-A_2 from Table I was used in a Wilcoxon Signed Rank test.

A_1-A_2 +1 0 +2 7 0 +9 0, +13 8 −2 8 +7 4 +3 6

Ranks 1 2 6, 7 −3 5 4

A_1-A −9 1 −9 6 +1 9 +2 2 −23 8 −14 6 −23 9 −11 0

A_2-A −1 4 −12 8 −5 1 −1 8 −8 3 −12 6 −16 5

The appropriate statistic is T which is the absolute value of the sum of the negative ranks. The 0 05 cut-off point is 2 so that this value of T = 3 is *not* statistically significant at the 0 05 level. Hence the hypothesis of *no* cumulative effect has not been rejected at the 0 05 level

B To test whether there was a drop in acetyl strophanthidin tolerance in the presence of hypomagnesemia, the data A_1-A_3 from Table I was pooled with A_2-A_3 from Table II The Wilcoxon Signed Rank test was used again The appropriate ranks are as follows

A_1 A − −8 3 4 −14 −12 −15 −9

A_2-A_3 −1 −11 −5 −2 −6 −10 −13

In this instance T = 7 The 0 05 cut off point is 25 so that this *is* statistically significant at the 0 05 level. The hypothesis of *no* drop in acetyl strophanthidin tolerance has been rejected

C To determine if the difference in means if the toxic amount of acetyl strophanthidin is directly related to the decrease in serum magnesium the question arises as to what effect the elimination of the magnesium removal as a concomitant variable will have on the difference in means in acetyl strophanthidin tolerance We used the values of A_1 A_3 and A_4 in Table II pooled with the values of A_1 A_2, and A_3 in Table III (Table A)

$F_{2, 27}$ = 5 0184 > 3 35 (significant at the 5 per cent level) This F value is significant.

Next an analysis of covariance was performed to eliminate the effect of the magnesium removal The data are listed in Table B

$F_{2, 26}$ = 150 7092/104 233 = 1 446 This is not significant. The estimated slope of the regression is (4 221)/2 0469 = 2 0627 The adjusted means for the toxicity tolerance becomes for

I 47 4 − 2 0627 (1.513 − 1 053) = 46.45
II 36 81 − 2 0627 (0.903 − 1 053) = 37 12
III 33.89 − 2 0627 (0 744 − 1 053) = 34.53

Since these adjusted means are *not* significant, the removal of the magnesium effect has removed the differences in acetyl strophanthidin tolerance

*The following references were consulted

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Serum creatine phosphokinase activity following isoproterenol induced myocardial infarction in male and female rats with and without arteriosclerosis

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Changes in serum enzyme levels have become very valuable indicators of the severity and temporal progression of myocardial infarction and other conditions. The clinical diagnostic value of serum enzyme changes is somewhat compromised by the relative lack of specificity of the various enzymes used, e.g., transaminases, glutamic oxaloacetic and pyruvic (SGOT and SGPT respectively) and lactic dehydrogenase (LDH). These enzymes lack specificity because they are also present in organs other than the heart, e.g., in the liver and red blood cells, so that increased serum levels of these enzymes may reflect hepatic necrosis or red blood cell lysis in addition to myocardial necrosis. The enzyme, creatine phosphokinase (CPK), is of particular current interest because it is purported to be much more specific than the other enzymes currently used. CPK has been found in high concentration in cardiac and skeletal muscle with a lesser amount in brain tissue but no CPK has been detected in red blood cells, liver, lung, or kidneys.[1-4] Creatine phosphokinase catalyzes the reversible transfer of high energy phosphate from adenosine triphosphate to creatine. Serum CPK levels are markedly elevated during myocardial infarction particularly during the earliest stages of myocardial ischemia and necrosis.

The potent catecholamine and beta adrenergic stimulating agent, isoproterenol, will produce minimal to massive myocardial infarction in animals depending on the dose employed.[4] In previous work, we have found that there is a very dramatic rise and fall in serum SGOT, SGPT, and LDH following isoproterenol induced myocardial infarction in rats. The degree of rise and fall in serum enzyme activity is commensurate with the extent of the myocardium infarcted. Further, we had also found that the pattern of change in serum enzymes following myocardial necrosis was quite different between rats having arteriosclerosis and those which had normal arteries.[4] Although the determination of serum CPK activity is beset with certain technical problems, we were able to adapt an automated method for the multiple and accurate determination of this relatively unstable enzyme. The experiments

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A_1-A_4 −7 −8, 3 4 −14 −12 −15 −9

A_1-A_3 −1 −11 −5 −2 −6 −10 −13

In this instance T = 7 The 0 05 cut off point is 25 so that this is statistically significant at the 0 05 level The hypothesis of *no* drop in acetyl strophanthidin tolerance has been rejected.

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Several seemingly paradoxical findings observed by us previously[n n] and again in these experiments presented themselves. Although the female rats, arteriosclerotic and nonarteriosclerotic outwardly manifested the most severe evidence of prostration shock and heart failure they nonetheless survived in significantly greater numbers than their male partners. Similarly the female rats also showed much more rapid and effective myocardial repair than their male cohorts. Perhaps even more intriguing and provocative is our consistent observation in this and in our other work that animals with the seeming disadvantage of pre-existing arteriosclerosis prior to the dynamic challenge of a myocardial infarct fare better outwardly and survive in greater numbers than their brothers and sisters with healthy or uncompromised arteries.

Confirmation of presence or absence of pre-existing arteriosclerosis prior to and during myocardial infarction None of the virgin animals, male or female used in these experiments showed any evidence of arteriosclerosis. Only 10 per cent of the male breeders manifested grossly visible calcific plaques in their iliac arteries. Of the 120 arteriosclerotic female rats which survived myocardial infarction and whose CPK levels are shown in Fig 2 38 were classified as having "clear aortas at autopsy 23 were minimal i.e. lesions in the abdominal aortic segment only 43 were moderate i.e lesions in the abdominal and arch segments, and 16 were severe i.e extensive grossly visible calcific plaques throughout the aorta. In each of the sequential time groups put to death there was a good representation of graded degrees of severity of arteriosclerosis e.g one or two animals having a clear aorta, a "minimal and 3 moderate and possibly one subject having a severe" aorta. Thus, we were able to compare the dynamics of the response of serum CPK in subjects with and without arterial disease during the active stages of myocardial destruction.

Creatine phosphokinase

MALES Serum CPK levels rose promptly and significantly within an hour after injection of isoproterenol i.e. beginning myocardial necrosis (Fig 1) The level of serum CPK continued to rise dramatically reaching a peak 24 hours later The arteriosclerotic and nonarteriosclerotic animals showed the same prompt rise and peak of serum CPK levels. In the case of the two special groups included to test for CPK levels *48* hours after a single injection of isoproterenol without any further treatment CPK levels were found to have returned to almost normal levels commensurate with the animal's resumption of apparently normal activity (Fig 1)

reported here demonstrate (1) very dynamic increases in serum CPK levels following myocardial necrosis (2) the diverse nature of serum CPK levels between male and female rats following myocardial necrosis and (3) the pattern of serum CPK response between animals with and without arteriosclerosis prior to the induction of myocardial necrosis

Materials and methods

All of the animals used in these experiments were Sprague-Dawley rats of the original Sprague Dawley strain Male and female virgin rats were used as subjects having no pre-existing arterial disease Male and female breeder rats were used as subjects known to have pre-existing arteriosclerosis.[7,10] The female breeder rat develops grossly visible arteriosclerosis the male breeder rat develops grossly visible plaques in their iliac arteries and only microscopic lesions in the aorta [7] However the arterial lesions ramify outward in both sexes into the coronary [8] carotid [9] renal [10] mesenteric [10] and peripheral arteries.[10] The nonarteriosclerotic virgin rats used in the present study were mature and comparable in age to the arteriosclerotic rats

A large number of the nonarteriosclerotic male and female virgin rats were given a single subcutaneous dose of 50 mg of isoproterenol per 100 grams of body weight dissolved in saline Animals were put to death by instant decapitation rather than by anesthesia to avoid stress 1 2 3 4 5 6 12 24 and 48 hours later This last group was included to determine the effects of the first (and a single) injection of isoproterenol on serum CPK levels when taken two days later without further intervention or treatment. Twenty four hours after the first injection (start of Day 2) all of the surviving animals except the 48 hour group described above were given a second injection of isoproterenol on the same dose per body weight basis and the animals put to death 1 2 3 4 5 6 12 and 24 hours later One final group was allowed to recuperate for 8 days after the second injection A minimum of 6 animals was put to death at each of the time intervals listed above

The identical regimen of injection and autopsy was followed in the case of the arteriosclerotic male and female breeder rats. However a smaller dose of isoproterenol 25 mg per 100 Gm of body weight given subcutaneously was used The reduced dose of isoproterenol in the case of the arteriosclerotic rats is required to insure the survival of a sufficient number of arteriosclerotic animals. Despite the lower dose given the arteriosclerotic rats, the area of myocardium infarcted and all of the characteristics of its gross and microscopic pathology appear to be identical to those of the nonarteriosclerotic rats given twice the dose of isoproterenol

Male and female arteriosclerotic rats and male and female nonarteriosclerotic rats, 12 of each kind were sacrificed 4 hours after having been given a placebo injection of saline These animals were to serve for purposes of establishing baseline data for comparison purposes

At autopsy blood was collected from the severed neck vessels centrifuged and the serum separated for CPK determination Creatine phosphokinase was measured by a modification of the automated fluorometric method of Willis and associates[11] using the Auto-analyzer (Technicon) Because of the paucity of information concerning serum CPK levels in rats a special and separate study had to be made of normal serum levels in male and female rats. Unlike those in the human serum CPK levels were found to be higher in female than in male rats. The CPK enzyme activity was expressed in Sigma units 1 Sigma unit = μM per milliliter of creatine $\times$ 20 [11]

The aorta of each animal was carefully inspected for the presence or absence of arteriosclerosis. Final body and heart weights were recorded Key organs were saved for histopathologic study (to be reported separately)

Results

General observations The isoproterenol injected animals developed the typical signs of myocardial infarction which we have observed in the past.[8,9] The animals became prostrate and stuporous, and they evinced intense tachycardia and deep abdominal breathing This clinical picture of myocardial infarction appeared within minutes of administration of the first in

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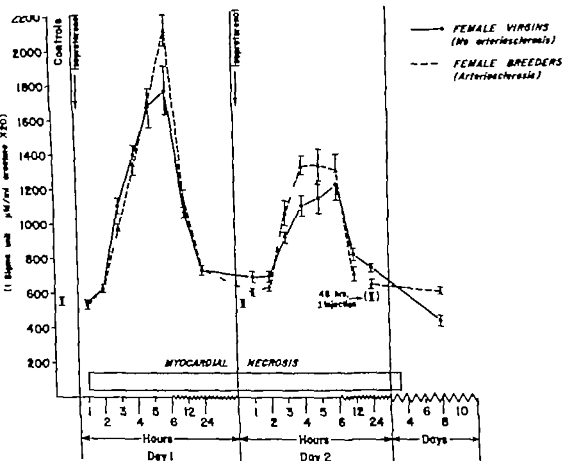


Fig. 2 Change in serum CPK levels (mean ± standard error) of arteriosclerotic and nonarteriosclerotic female Sprague-Dawley rats at various time intervals after two injections of isoproterenol spaced 24 hours apart. (CPK levels show separately 48 hours after the first injection of isoproterenol are included to demonstrate the drop in CPK, in time, if only one injection of isoproterenol is given.) Myocardial necrosis is an ongoing event and becomes maximal between the second and third day. Myocardial repair is rapid and occurs between the fourth to the tenth day.

Although the CPK levels began to rise again after the second injection of isoproterenol, the overall response was not as great as the response observed after the first injection (cf Figs. 1 and 2). Again as in the case of the male subjects, the female rats with pre-existing arterial disease achieved higher levels of CPK than their sisters with normal arteries. By the close of the experiment a week after the initial onslaught of myocardial necrosis, and when myocardial repair was ostensibly affected the female rats with intact arteries displayed normal CPK levels while arteriosclerotic animals showed nearly normal levels (Fig. 2).

When the serum CPK values were compared between male breeders with and without arterial lesions in their iliac arteries, there was no discernible difference which could be ascribed to the presence or absence of arterial damage. Similarly when the CPK data was grouped according to the degree of severity of grossly visible arterial disease there was no correlation whatsoever between severity of arterial disease and serum CPK levels. For example, the average CPK level for all of the female breeders having clear aortas was 914 ± 6 for the minimal group 1016 ± 12 moderate 898 ± 4 and severe 910 ± 5 (mean ± standard error) i.e. there were

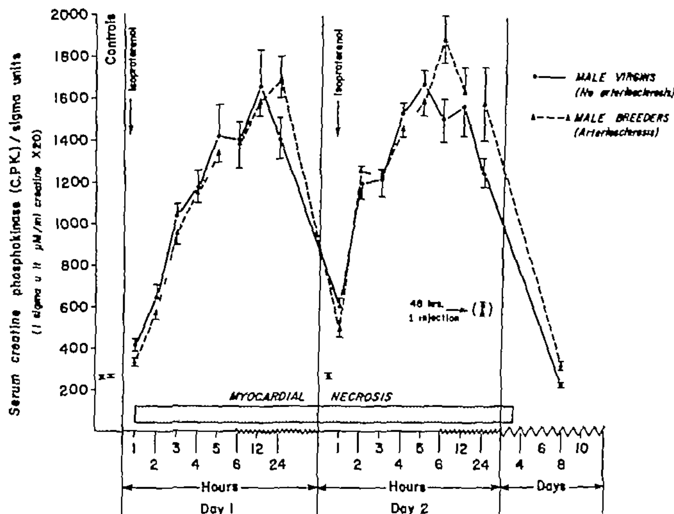


Fig 1 Changes in serum CPK level (mean ± standard error) of arteriosclerotic and nonarteriosclerotic male Sprague-Dawley rats at various time intervals after two injections of isoproterenol spaced 24 hours apart. (CPK levels shown separately 48 hours after the first injection of isoproterenol are included to demonstrate the drop in CPK in time, if only one injection of isoproterenol is given.) Myocardial necrosis is an ongoing event and becomes maximal between the second and third day. Myocardial repair is rapid and occurs between the fourth to the tenth day.

Following the second injection of isoproterenol and despite the ongoing myocardial necrosis, i.e. based on histopathologic criteria, the almost normal CPK levels began *to rise again promptly and precipitously.* With this second bout of exposure to intensified myocardial necrosis, CPK levels rose to a maximal new height within 5 to 6 hours. At this apogee of serum CPK increase there was a questionable separation of CPK levels between arteriosclerotic and nonarteriosclerotic males, with arteriosclerotic animals evincing the greatest CPK increase (Fig 1). Otherwise the pattern of CPK change was very much the same, returning to normal levels 8 days after the inception of myocardial necrosis and at a time when the myocardium was ostensibly completely repaired.

FEMALES. The serum CPK increase in females was prompt but not as acute as in males, *i.e. a significant increase in CPK levels did not occur until 2 hours after the first injection of isoproterenol* (Fig 2). On the other hand, unlike the males, the CPK levels of females reached a peak within 6 hours after being challenged with *isoproterenol and achieved elevation of* CPK levels well above the highest levels reached by the male subjects (cf Figs. 1 and 2). The elevated levels of serum CPK in arteriosclerotic and nonarteriosclerotic females were short lived, *falling precipitously back to normal 12 to 48 hours after* the first injection of isoproterenol (Fig 2).

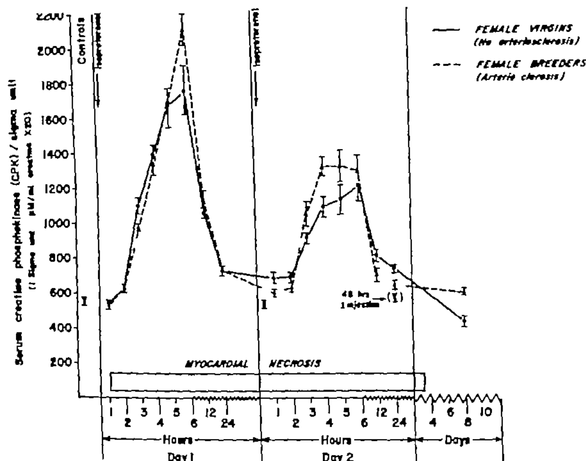


Fig. 2. Change in serum CPK levels (mean ± standard error) of arteriosclerotic and nonarteriosclerotic female Sprague-Dawley rats at various time intervals after two injections of isoproterenol spaced 24 hours apart. (CPK levels shown separately 48 hours after the first injection of isoproterenol, are included to demonstrate the drop in CPK, in time, if only one injection of isoproterenol is given.) Myocardial necrosis is an ongoing event and becomes maximal between the second and third day. Myocardial repair is rapid and occurs between the fourth to the tenth day.

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no significant differences in CPK levels which could be related to the severity of arteriosclerosis.

Changes in heart weight in subjects with and without coexisting arteriosclerosis and myocardial infarction The average body weight of both male and female breeder rats ranged from 50 to 100 grams more than their virgin counterparts This difference in body weight was due to the unusual adiposity of the arteriosclerotic breeder rats The hearts of arteriosclerotic breeder rats were also substantially heavier than virgin rats of their same age The heavier hearts of the arteriosclerotic rats have been attributed to the hypertension which the animals develop

The absolute weight (or the ratio of

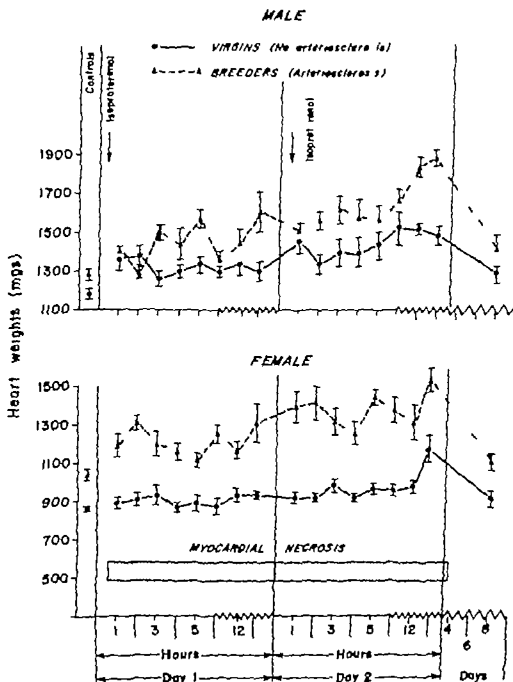


Fig 3 Changes in heart weight (mean ± standard error) of male and female Sprague-Dawley rats with and without arteriosclerosis, at various time intervals, after two injections of isoproterenol spaced 24 hours apart Myocardial necrosis is an ongoing event and becomes maximal between the second and third day Myocardial repair is rapid and occurs between the fourth to the tenth day

heart weight to body weight) of the animals under investigation showed a prompt and decided increase one hour after the first injection of isoproterenol (Fig. 3). Heart weights showed dynamic oscillations hour by hour but the trend was definitely in the direction of increased weight. Although the heart weights of arteriosclerotic animals were considerably heavier than the nonarteriosclerotic animals the overall pattern of change for each group was parallel and very much the same.

Although the serum CPK levels had returned to normal levels 24 to 48 hours after the first injection of isoproterenol the hearts continued to be increased in weight consonant with the gross and histologic evidence of ongoing and persistent myocardial necrosis during these two days and at this particular time period.

Following the second injection of isoproterenol the heart weights of both groups of arteriosclerotic and nonarteriosclerotic animals continued to show their upward trend (Fig. 3). However, the female rats, having severe arteriosclerosis, showed the most sustained and greatest increase in heart weight following the second injection of isoproterenol (Fig. 3). By the close of the second day the male breeder rats with relatively mild arteriosclerosis also manifested a considerable increase in heart weight compared to their nonarteriosclerotic brothers (Fig. 3). Within the week when gross and histopathologic evidence indicated that the heart damage was essentially completely repaired, nonetheless the weight of the hearts of all experimental animals was persistently above normal (Fig. 3).

Histopathology. The details of the gross and histopathologic changes in the hearts of these animals will be reported separately. Pertinent to this report, it should be noted that the most extensive evidence of myocardial necrosis, confirmed by histologic examination, coincided with the peak of serum CPK levels observed in the arteriosclerotic males 5 to 6 hours after their second injection of isoproterenol (Figs. 1, 4, and 5). Similarly, CPK levels were back to normal coincident with histologic evidence of cessation of myocardial destruction. However, there were certain discrepancies between myocardial histopathology and CPK levels in the sense that increase in serum CPK levels is a sensitive index of cardiac necrosis. First, the serum CPK levels began to rise, substantially, within an hour after injection of isoproterenol (Figs. 1 and 2). At this time, the histologic sections showed no evidence of myocardial cell lysis or damage except for beginning interfascicular cardiac edema. Histologic evidence of necrosis did not appear until 5 to 6 hours later. Thus, it appears that the serum CPK level is, indeed, a very sensitive index of myocardial destruction. Second, however, during the interim between the first and second injections of isoproterenol when the CPK levels began to drop toward normal (Figs. 1 and 2), i.e., 48 hours after isoproterenol, microscopic examination of the myocardium of these animals showed no apparent cessation in the progressive increase, hour by hour, of myocardial destruction. Therefore, it would appear that the CPK levels were reduced almost to normal despite what appeared to be histologically active and continuous cardiac necrosis.

Discussion

One of the most outstanding findings of this experimental investigation is the prompt and dynamic nature of the response of serum CPK levels to the degeneration and necrosis of myocardial muscle. The serum enzyme changes which we have observed pertaining to transaminases (SGOT and SGPT) and lactic dehydrogenase (LDH) in rats during the acute stages of myocardial infarction are also quite dramatic. For example, SGOT levels rise by 220 per cent during the first 24 hours of isoproterenol induced myocardial infarction. However, neither the SGOT or SGPT changes show any of the hour by hour substantial increases manifested by CPK nor do they approach the CPK test in the degree to which it peaks within the first 24 hours of an infarct, i.e., 800 per cent. The serum LDH levels in rats undergoing active myocardial destruction do not rise as steeply nor as promptly as the SGOT and SGPT levels. This same situation obtains in man and although SGOT and SGPT are good indicators of the extent of myocardial necrosis during the acute stages of a myocardial infarct, clinically



Fig 4 Cross section of the apex and left ventricle of the heart of an arteriosclerotic male 5 to 6 hours after a second injection of isoproterenol when serum CPK reached maximum levels. There is extensive confluent necrosis throughout the apex and into the left ventricle The light grey area in the photo (marked A) is viable myocardium, all of the granular area (marked B) necrotic myocardium showing massive cellular infiltration and complete destruction of all muscle fiber in this area of infarction (Hematoxylin and eosin. X75)

LDH is a better index of the later stages of progression of an infarct.[14] Our findings which indicate that serum CPK levels afford a more dynamic index of myocardial infarction than serum SGOT and LDH levels are in agreement with the findings of those who have used this enzyme clinically [1-8 11 13 14] Our use of experimental animals and our ability to sacrifice animals on an hour by hour basis during and after the development of a myocardial infarct reinforces this contention

The specificity of serum CPK activity further attests to its usefulness as an index of myocardial *infarction* Although muscular exercise will cause elevation of serum CPK, it must be of the particularly strenuous variety and in nonathletic subjects to elicit a response in serum CPK comparable to what is observed in myocardial infarction [1] The CPK activity of the brain could contribute to serum CPK levels following myocardial infarction but to date no substantial increases in serum CPK levels have been observed in patients after cerebrovascular accidents. Furthermore it has been found that serum CPK levels do not rise in patients having hepatitis acute or chronic pulmonary infarction angina pectoris or congestive heart failure.[15] In cases of liver involvement or congestive heart failure the other enzymes used to detect myocardial necrosis, such as SGOT SGPT and LDH would be elevated due to the contributions of the liver to overall enzyme levels or LDH released from hemolyzed red blood cells. This was also borne out in our experimental model in that the induced massive myocardial infarcts also elicited hepatic necrosis and fatty infiltra



Fig. 5. Higher power view of an infarcted heart from an arteriosclerotic male 5 to 6 hours after second injection of isoproterenol when serum CPK reached maximum levels. The light gray and striated tissue (marked *A*) in the photo shows the island of still viable myocardial tissue surrounded by granular necrotic tissue (marked *B*). The arrows point to isolated strands of surviving cardiac muscle. Notice the abrupt, open, and jagged ends of the muscle fibers where active dissolution of sarcoplasm is taking place. (Hematoxylin and eosin. ×180.)

tion as well as severe hydrothorax without the latter conditions contributing to the overall CPK levels. This was shown by the fact that breeder rats having fatty livers along with their arteriosclerosis, showed no level of CPK activity which would approach the levels found during myocardial necrosis. Also the serum CPK levels began to rise promptly and hours before we observed any evidence of pulmonary edema or fluid accumulating in the thorax.

It is of interest that although female rats appear to show more severe prostration at first than male rats, they recover faster, repair their myocardium more speedily and survive in much greater numbers. This sex difference in response to infarction also appears to be reflected in the serum CPK pattern since, although the females showed a very prompt and substantial rise in CPK levels after the first injection there was a comparatively modest response in CPK activity following the second injection of isoproterenol.

It is also of interest that the presence of arteriosclerosis, even severe grossly visible calcific arteriosclerosis in the case of female breeders, prior to and during the course of myocardial infarction, did not contribute in any way to serum CPK levels. This would indicate that arteriosclerosis per se in patients experiencing cardiovascular difficulties probably does not contribute to the serum CPK level.

The changes in heart weight during the acute stages of myocardial necrosis were particularly manifest in the male rats and

were certainly most pronounced in animals having arteriosclerosis. This increase in heart weight is probably due to the edema cellular infiltration and other factors during the establishment of the infarct Stanton and associates[17] showed that isoproterenol will produce cardiomegaly in rats with cardiac edema and increase in cardiac protein and nucleic acids. However this was after chronic injection of isoproterenol and at much lower doses than we employed Mueller and Axelrod[18] have shown that there is a great disturbance in myocardial electrolytes in rats subjected to the infarct inducing effects of isoproterenol This electrolyte disturbance and concomitant disturbances in cardiac neuronal impulse transmission could be corrected by treatment with a ganglionic blocking agent by salt restriction mercurial diuresis or withholding isoproterenol[18] In separate studies we have shown that arteriosclerotic rats become less capable of converting steroid precursors such as 18 hydroxy-desoxycorticosterone to the definitive salt and electrolyte-regulating hormone aldosterone[19] However during isoproterenol induced myocardial infarction although there is a definite shift in adrenal steroid biosynthesis in favor of aldosterone production in all animals the arteriosclerotic animals, nonetheless show the greatest capacity to produce aldosterone[4] Thus there may be a direct connection between greater aldosterone production by arteriosclerotic rats myocardial electrolyte disturbance and the concomitantly greater cardiac weight increase in arteriosclerotic rats

From our studies reported here it would appear that actual destruction of the sarcolemmal membrane is not paramount to CPK release Apparently alteration in the permeability of the myocardial sarcolemmal membrane is sufficient to permit CPK release This is of special interest since this would indicate that actual muscle cell necrosis is not essential for CPK release and factors like catecholamines, steroids local hypoxia ground substance factors or electrolytes may act on the cellular membrane increasing its permeability and efflux of cytoplasmic enzymes. Wagner and Critz[18] have shown that glucocorticoids will stabilize the cell membrane reduce its permeability and prevent CPK leakage. This is particularly provocative since we have found a decided drop in adrenal glucocorticoids during the early onset of myocardial necrosis in isoproterenol treated rats.[4] This may explain the prompt increase in serum CPK activity despite little or no histopathologic evidence of myocardial necrosis that is, the CPK increase is due to increased myocardial cell permeability conditioned by the abrupt and simultaneous reduction in glucocorticoid biosynthesis under conditions of myocardial hypoxia

Summary

Male and female rats with and without arteriosclerosis were given two subcutaneous injections of isoproterenol spaced 24 hours apart. The animals promptly developed signs of shock and prostration and myocardial infarction Sequential sacrifice of the animals at hourly intervals after each of the injections of isoproterenol demonstrated that there was a prompt and marked increase in serum creatine phosphokinase (CPK) activity commensurate with the destruction of myocardial tissue Serum CPK levels were elevated long before microscopic examination of the myocardium could demonstrate any evidence of overt muscle damage indicating that the enzyme CPK is a sensitive index of not only myocardial necrosis but of sarcolemmal membrane permeability as well The changes in serum CPK levels were much more dramatic in these experiments than in previous experience where other serum enzymes were used to detect myocardial infarction e g transaminases (SGOT and SGPT) and lactic dehydrogenase Female rats showed much more severe untoward signs in connection with myocardial infarction than males. Yet the female subjects survived in much greater numbers and showed much more rapid and effective repair of the heart than the male subjects. This dichotomous response between the sexes was also reflected in the pattern of the CPK response. Animals having pre-existing arteriosclerosis prior to being subjected to isoproterenol induced myocardial infarction show greater excursion of their serum CPK levels than animals with normal arteries. However

the presence of severe arteriosclerosis per se in no way contributed to serum CPK levels. Therefore, it is suggested that the extra elevation of serum CPK levels in arteriosclerotic animals is a reflection of greater intrinsic damage to the myocardium in such subjects despite the fact that they manifest less severe evidence of shock and heart failure than subjects with normal arteries. Heart weight is greatly increased during the acute episode of myocardial infarction with marked oscillations in weight on an hour-by hour basis. Histologic and other evidence indicates that this increase in cardiac size and weight is due to cellular infiltration edema and possible myocardial electrolyte abnormalities, and increased sarcolemmal membrane permeability.

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Effects of cardiac glycosides on the abnormal pulmonary circulation of the dog

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Hemodynamic effects of cardiac glycosides have been studied extensively in patients with compensated hearts and in those with congestive cardiac failure[1,2] Cardiac glycosides increase myocardial contractility decrease the heart rate and produce generalized vasoconstriction[4] Previous studies have shown that cardiac glycosides especially acetyl strophanthidin induce pulmonary vasoconstriction[5,7] Clinically cardiac glycosides are often used in patients with congenital heart disease and increased pulmonary blood flow so the increase in pulmonary vascular reactivity with increased pulmonary blood flow may have clinical pertinence Specifically digitalis-induced pulmonary vasoconstriction may increase right ventricular work and decrease left-to-right shunting This report concerns the effects of acetyl strophanthidin and digoxin on the pulmonary and systemic circulations of the unanesthetized dog with absolutely and relatively increased pulmonary blood flow A new hypothesis is offered to explain the increased pulmonary vasoreactivity found with increased pulmonary blood flow

Methods

Under sterile conditions left thoracotomy was performed in ten anesthetized mongrel dogs weighing between 18 to 25 kilograms. Polyvinyl catheters (inner diameter 1 mm) were secured in the left atrium main pulmonary artery and aorta and were filled with heparin to prevent clotting[11] An electromagnetic flow probe was placed around the main pulmonary artery The left pulmonary artery was ligated securely close to its origin to divert all pulmonary blood flow through the right lung In one dog a prosthetic tunnel with an externally adjustable occluding balloon[12] was sewn between the aorta and pulmonary artery instead of ligation of the left pulmonary artery In this dog pulmonary blood flow was increased by balloon deflation and an electromagnetic flow probe was placed around the ascending aorta All catheters and flow probe wires were tunnelled subcutaneously to exit at the back of the dog's neck Dogs were permitted to recover from the operation for seven to ten days during which time they were trained to lie quietly in a specially

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constructed box to permit pressure and flow measurements.

The protocol for experiments was the same as that used during previous studies of dogs with bipulmonary blood flow.[4] Only one drug was tested during any 24 hour period. No premedication was used. The dog was monitored until hemodynamic measurements stabilized for 10 to 20 minutes. Then pulmonary artery, left atrial and systemic arterial pressures and pulmonary blood flow were measured continuously during a 10 minute control period. At the end of the control period either acetyl strophanthidin, 40 μg per kilogram (13 experiments in dogs with a ligated left pulmonary artery and 6 experiments in a dog with aortopulmonary shunt) or digoxin, 50 μg per kilogram (9 experiments in dogs with ligated left pulmonary artery) was infused into the pulmonary artery. Pressures and flows were recorded continuously for 40 minutes subsequent to acetyl strophanthidin infusion and for 80 minutes after digoxin injection. Frequent measurements of arterial pH, pCO_2 and pO_2 were performed which confirmed the stability of oxygenation and acid base balance.

Catheters were connected to Statham P23BB strain gauges to measure left atrial and pulmonary arterial pressure. A P23DE transducer was used to measure systemic arterial pressure. Outputs of these strain gauges were amplified by Lexington 101A amplifiers. Mean pressures were obtained by electrical integration. Amplifier outputs were recorded on a Honeywell 1620 oscillograph. Peak stroke velocity (S Vel) was measured directly. Pulmonary blood flow or right cardiac output (CO) was obtained by electrical integration of stroke velocity and indexed per square meter of body surface area using Rubner's modification of Meeh's formula (1879), i.e., area in square meters = 0.112 (weight$^{2/3}$ in kilograms) so that results in dogs of different sizes could be compared. Pulmonary vascular pressure gradient (PVPG) was computed by subtracting mean left atrial pressure (LAP) from mean pulmonary artery pressure (PAP). Pulmonary vascular resistance (PVR) was computed by dividing PVPG by CO. Total systemic vascular resistance (SVR) was computed by division of systemic arterial pressure (SAP) by CO. Stroke volume (S Vol) was calculated by division of CO by heart rate (HR). Stroke work (S Wrk) was calculated by multiplying SAP and S Vol. Data for each parameter each minute after injection were compared to control levels. Percentage deviations following injection were determined by comparing each experimental minute value to its mean control. For LAP absolute change rather than percentage deviation was plotted. The mean changes were analyzed to test for statistical significance at intervals of 1, 2, 3, 5 and 10 minutes. A two-tail t test ($p < .05$) was computed to determine the significance of each mean change with respect to its control value.[12]

Since LAP and CO both changed when acetyl strophanthidin was administered it was necessary to determine what part of the change in PVR was due to vasoconstriction and what part was induced or

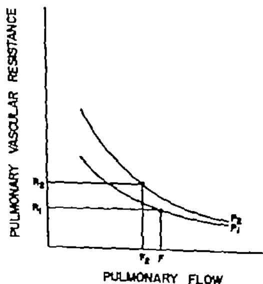


Fig. 1. Relationship of pulmonary vascular resistance (PVR) to pulmonary blood flow (CO) and left atrial pressure (LAP) is shown schematically. Open circle shows control values of LAP (P_1) and CO (F_1), giving predicted PVR (R_1). Closed circle shows LAP (P_2) and CO (F_2) following cardiac glycoside administration, giving predicted PVR (R_2). Passive per cent change in PVR (ΔRp) due to changes in CO and LAP was calculated by the formula

$$\Delta Rp = \frac{R_2 - R_1}{R_1} \times 100$$

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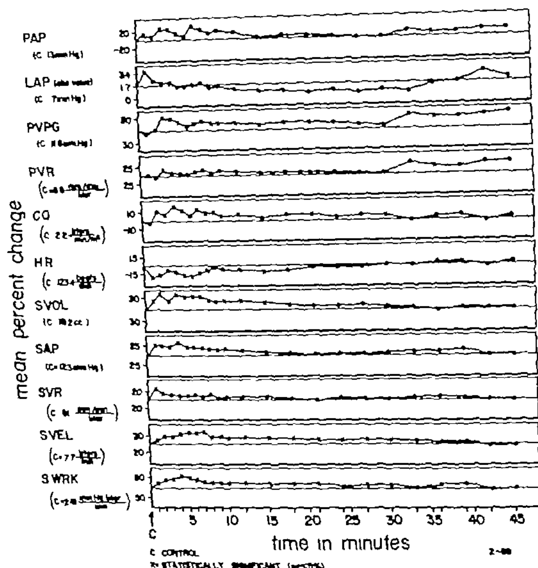


Fig. 2. Mean per cent changes in hemodynamic parameters (vertical axis) in minutes after injection of acetyl strophanthidin (horizontal axis). Summary of all experiments on the effects of acetyl strophanthidin (40 μg per kilogram) on abnormal pulmonary circulation. The zero line for each parameter represents the mean control level for that measurement. Absolute mean control values are printed at the left of each individual graph. All values are depicted as percentage change from control except for left atrial pressure, which is plotted in absolute values in millimeters of mercury. Mean changes for the designated time period are indicated by a black dot; those statistically significant at 5 per cent level are shown by a cross. See text (under Methods) for meaning of abbreviations.

LAP especially during the initial 5 minutes. Pulmonary arterial pressure increased about 25 per cent during the first 3 minutes and then returned to its control level. Because the increase in PAP was larger than the increase LAP, PVPG increased but the greater increase in CO caused a decrease in calculated PVR.

Digoxin was injected into the pulmonary artery in nine dogs with a ligated left pulmonary artery and relatively increased pulmonary blood flow. Statistically significant changes occurred in HR (10 to 15 per cent decrease) and S Vol (10 per cent increase). Systemic arterial pressure and SVR increased 5 to 10 per cent but this change was not significant. Pulmonary arterial pressure, LAP, CO and PVR did

masked by passive changes in pulmonary blood flow or LAP For this reason observed changes were compared to predicted PVR changes which would have resulted from changes in LAP and CO of the same magnitude if no vasoconstrictive agent had been administered Observed per cent change in PVR (ΔRo) following cardiac glycosides was corrected for passive change due to changes in CO and LAP as follows Data of Rudolph and associates[14] concerning PVR CO and LAP in normal open-chest dogs (their Figure 5A schematically shown in Fig 1) were used to predict the passive change in PVR with CO rescaled using cardiac index For example if CO decreased from point F_1 to point F_2 and LAP decreased simultaneously from curve P_1 to curve P_2 the passive vascular collapse would result in an increase in PVR from R_1 to R_2 If that magnitude of flow and LAP decrease was associated with a greater PVR increase than predicted one could conclude that pulmonary vasoconstriction had also occurred in addition to passive collapse Referring to this figure predicted passive change in PVR (ΔRp) was obtained by the following formula

$$\Delta Rp = \frac{R_2 - R_1}{R_1} \times 100$$

where ΔRp = per cent of change in PVR due to passive alteration R_1 = PVR predicted from observed LAP and CO during control period and R_2 = PVR predicted from observed LAP and CO at a given point in time following cardiac glycoside administration Corrected changes in PVR (ΔRc) were calculated by the following formula and were used to compare the effects of cardiac glycosides with normal and increased pulmonary blood flow

$$\Delta Rc = \Delta Ro - \Delta Rp$$

Results

Dogs with left pulmonary artery ligation had some dyspnea for a few days following operation but this disappeared in a week At the time of pharmacologic study these dogs were healthy and did not show dyspnea or other abnormal signs. Pulmonary arterial pressure was measured longitudinally following ligation of the left pulmonary artery Pulmonary arterial pressure was elevated but variable for one week following operation but remained stable during the period from two to eight weeks after operation when these studies were performed The average pressure in ten dogs following ligation of the left pulmonary artery was 14 mm Hg during this period Average of the mean PAP in fifteen intact, unanesthetized bipulmonary dogs was 12 mm Hg in our laboratory

At autopsy the ligated lungs were atelectatic and congested in animals who died during the first week postoperatively Those who survived the first week had expanded pale left lungs at autopsy

Thirteen experiments in five dogs with acetyl strophanthidin and nine experiments in seven dogs with digoxin were completed while dogs were lying quietly in a prone position In a small number of these experiments dogs developed nausea and vomiting as a result of the cardiac glycoside. Those records during body movement nausea or vomiting were carefully excluded and only those records in a quiet state were included for analysis. Complete results of acetyl strophanthidin in the unanesthetized dogs with ligated left pulmonary artery are shown graphically in Fig 2 and those in the dog with aortopulmonary shunt are shown in Fig 3

Acetyl strophanthidin was administered to dogs with ligation of the left pulmonary artery (with essentially doubled pulmonary blood flow to the right lung) In these dogs PAP increased about 20 per cent initially as CO increased slightly (+10 per cent) and LAP did not change significantly Pulmonary vascular pressure gradient increased and calculated PVR showed an increase of 10 per cent These effects decreased during the 30 minutes following injection Cardiac effects such as decrease in HR increase in S Vel and increase in SAP and SVR appeared the first minute after injection and persisted for over 20 minutes.

The dog with the open aortopulmonary shunt was in heart failure during the control period (note high LAP and tachycardia in Fig 3) Following injection of acetyl strophanthidin CO increased about 10 per cent and HR decreased for over 20 minutes Systemic arterial pressure increased and was accompanied by increased

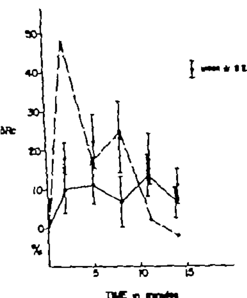


Fig. 4. Pulmonary vasoconstrictive effects of acetyl strophanthidin are compared among the dogs with normal blood flow (solid line), those with ligated left pulmonary artery (dotted line), and the dog with aortopulmonary shunt (broken line). Corrected change in PVR (ΔRc, see text under Methods) (vertical axis) in minutes after injection of acetyl strophanthidin (horizontal axis) is plotted. Statistically significant points compared with those in normal pulmonary blood flow are shown with cross ($p < 0.05$) and as open circle ($0.05 < p < 0.10$).

after injection and returned to the control level by 12 minutes after injection. The increase in this dog was statistically significant at 2 minutes after injection compared with the group with normal pulmonary blood flow or those with a ligated left pulmonary artery.

Discussion

Vasoconstrictor and vasodilator responses of pulmonary blood vessels to pharmacologic agents are of major interest. As has been shown by Rudolph and associates,[14] calculated PVR changes passively with changes in blood flow, LAP, and alveolar pressure. These passive changes in vascular resistance make it difficult to evaluate an active increase in the tone of pulmonary blood vessels following injection of pharmacologic agents in intact animals. To surmount this difficulty, we calculated the passive change in PVR due to change in the LAP and CO to predict the passive change (ΔRp) and subtracted this predicted passive change from the observed change in PVR (ΔRo) to get a corrected change in PVR (ΔRc).

The chronic instrumented dog with a ligated left pulmonary artery presents a unique hemodynamic condition. In comparison with the chronic instrumented dog without ligation, the dog with ligation has approximately twice as much blood flow to the right lung and no apparent change in CO, LAP, or SAP. Pulmonary arterial pressure may be slightly but not significantly higher in some dogs with ligation but the increase is usually minimal in the time period studied here. Adequate ventilation and expansion of the right lung is maintained. Therefore, this preparation permits us to study the possible difference in pulmonary vascular reactivity due to increased pulmonary blood flow in a physiologic state.

The cardiac and systemic hemodynamic effects of acetyl strophanthidin in dogs with ligated left pulmonary artery were qualitatively similar to effects in dogs with normal pulmonary blood flow, except that CO showed a slight increase (about 10 per cent) for 10 minutes following injection of acetyl strophanthidin in this study. Change in the LAP was different in these two groups. In normal dogs, the LAP decreased 2 to 4 mm. Hg following administration of acetyl strophanthidin, and this fall in LAP would theoretically increase PVR by 10 to 20 per cent by collapse of pulmonary veins.[14] The decrease in LAP was less than 1 mm. Hg in the group with relatively increased flow; therefore, the passive effect on PVR was smaller. Pulmonary vascular resistance increases passively as the LAP decreases and CO decreases.[14] These two factors were more apparent in our early study of the effects of acetyl strophanthidin in normal dogs, and less apparent or reversed in the present study of dogs with a ligated left pulmonary artery, making the comparison of change in PVR difficult. Correction of PVR for passive changes permits direct comparison of active effects of acetyl strophanthidin on PVR in these two groups. Increase in PAP was more apparent in the relatively increased flow group than in the normal flow group, and corrected PVR increased more following acetyl strophanthidin injection in the increased flow group than

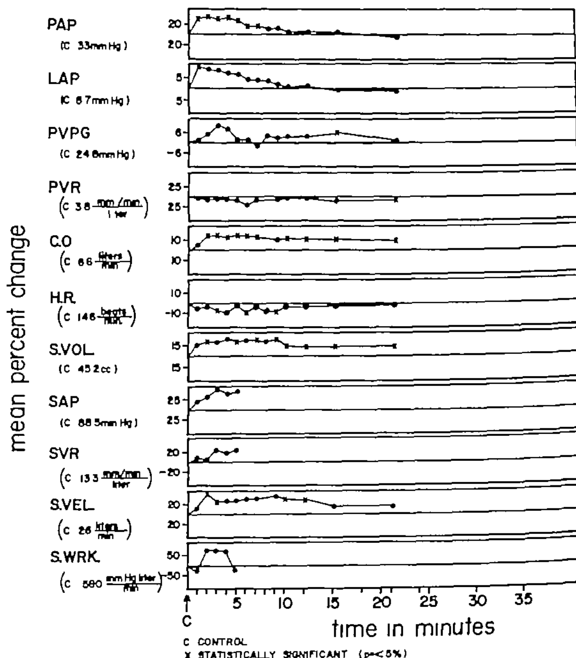


Fig 3 Mean changes in hemodynamic parameters following injection of acetyl trophanthidin in the dog with aortopulmonary shunt. (Comments as in Fig 2)

not change during the 80 minute period of observation

In an effort to factor out passive change the corrected change in PVR was computed by subtracting predicted passive change from observed change in PVR. The results obtained from animals with normal and relatively and absolutely increased pulmonary blood flow are shown in Fig 4 The data in chronic instrumented awake dogs without pulmonary artery ligation in our early paper[4] were used for comparison In dogs with a ligated left pulmonary artery (dotted line) corrected PVR (ΔRc) increased significantly (compared to control values) from 2 to 14 minutes following administration of acetyl strophanthidin The magnitude of this increase was consistently greater than that seen in dogs with normal pulmonary blood flow (solid line) during an equivalent period The difference was significant at the eighth minute ($0.05<p<0.10$) but only approached it at other times because of large standard deviation and small number of animals. In the dog with aortopulmonary shunt corrected PVR (ΔRc) (broken line) increased markedly in the initial few minutes

striction was shown by increased pulmonary arterial pressure and pulmonary vascular resistance. Comparison of these with our early results in intact dogs with bipulmonary circulation revealed that acetyl strophanthidin produced a greater rise in pulmonary vascular resistance in dogs which have an increased ratio of blood flow to available pulmonary vascular bed. Hemodynamic effects of acetyl strophanthidin were also studied in a fully awake dog with an aortopulmonary shunt. An increased magnitude of pulmonary vasoconstriction produced by acetyl strophanthidin in dogs with relatively and absolutely increased pulmonary blood flow was apparent after correction for passive effects of increased pulmonary blood flow and increased left atrial pressure. These findings may have implications regarding one determinant of pulmonary vasoreactivity.

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in the normal flow group implying increased pulmonary vascular reactivity related to increased flow. A large increase in corrected PVR in a dog with an aorto-pulmonary shunt following acetyl strophanthidin injection is in agreement with this relationship.

Increased pulmonary vascular reactivity to hypoxia with increased pulmonary blood flow has been reported by Blount, Vogel and their group[10, 11] who produced hypoxic reactive pulmonary hypertension by ligating one pulmonary artery of newborn calves in Denver. They could also produce reactive pulmonary hypertension by ligating the right pulmonary artery of newborn calves at sea level where no apparent hypoxic stimulation was present.[10] In the neonatal period in all tested species the pulmonary vascular bed demonstrates high resistance and high reactivity to any stimulus.[16, 17] This high vascular reactivity regresses rapidly in the neonatal period and in adults pulmonary vessels have diminished reactivity.[17] In humans with congenital cardiac disease and left-to-right shunts increased pulmonary blood flow seems to be associated with increased pulmonary vascular reactivity. Vogel and associates[18] could demonstrate twice as much PVR in patients with ventricular septal defect in Denver than in similar patients in Houston. They thought this difference was due to hypoxic stimulation in Denver and that these patients with ventricular septal defects have a more reactive pulmonary vascular bed than healthy children whose PVR is only minimally increased in Denver.[19] They also showed that some patients with atrial or ventricular septal defect and increased pulmonary blood flow have such a reactive pulmonary vascular bed that mild hypoxia during sleep was associated with remarkable pulmonary hypertension.[20]

Length tension relationships in the heart muscle and skeletal muscle have been well known since Starling[21] and Lundholm and Lundholm[22] showed that the smooth muscle in vascular wall also acts according to Starling's law. Therefore active development of tension increases as the vascular circumference increases to some point but beyond this point active tension development decreases as the perimeter of the vascular wall is further distended. This was documented with the mesenteric artery but the same phenomenon has been observed in the pulmonary artery.[23]

In these animals with a ligated left pulmonary artery blood flow through the right lung is approximately doubled. Pulmonary arterial pressure is increased only minimally; therefore calculated control PVR in that lung decreased approximately to the half suggesting dilatation of the resistance vessels of that lung. We have shown increased pulmonary vascular reactivity following acetyl strophanthidin and other vasoconstrictive agents under these conditions.[24] This increased vascular reactivity with doubled blood flow may be explained by applying Starling's law to vascular smooth muscle and by assuming that normal and doubled pulmonary blood flow correspond to two points on the ascending limb of Starling's curve.

An alternative or additional explanation may be that with normal pulmonary blood flow some vessels are patent while others are collapsed in the less dependent portions of the lung.[25] When pulmonary flow or pressure is increased (as in pulmonary vasoconstriction) the collapsed vessels become patent,[24] increasing the total cross-sectional area of the pulmonary vasculature and thus decreasing the PVR. In contrast with relatively high pulmonary blood flow as in our dogs with ligated left pulmonary artery, most of the vessels are originally patent so that fewer "reserve" vessels are available for opening following vasoconstriction and PAP increase. Thus a pulmonary vasoconstrictive agent such as acetyl strophanthidin would cause a greater rise in PAP in a high flow state than in the normal flow state because of a lack of the "buffering" action of collapsed reserve vessels in the former condition.

Summary

Hemodynamic effects of acetyl strophanthidin were studied in fully recovered awake unsedated instrumented dogs with a ligated left pulmonary artery. Increased myocardial contractility, a negative chronotropic effect, and systemic vasoconstriction were indicated by increased cardiac output, slower heart rate, increased peak stroke velocity, and increased systemic arterial pressure and systemic vascular resistance. In addition, active pulmonary vasocon

ventricular muscle (infundibular region) was obtained from patients undergoing surgical correction of tetralogy of Fallot.

Rat heart muscle was obtained from Sprague-Dawley rats (180 to 220 grams) by the rapid removal of the heart and lungs after the rats were killed by a blow to the head. The heart and lungs were placed in cold oxygenated Krebs solution and the left atrium quickly dissected. (One third to one half was used for the experiments.) The left ventricle was opened and a papillary muscle arising from the submitral region and inserting in the apex was used in another group of experiments.

Anoxic stress and aerobic recovery of the heart muscle strips were induced as follows: (1) All muscle strips were placed in oxygenated (95 per cent oxygen/5 per cent carbon dioxide) Krebs solution at 37° C (or 24 to 28° C.) for 60 minutes. (2) Part of the muscle strips were subjected to anaerobic (95 per cent nitrogen/5 per cent carbon dioxide) Krebs solution for 60 minutes. The anaerobic Krebs solutions were maintained at 37° C. or 24 to 28° C. (3) After the anoxic stress, the muscle strips were allowed to recover for 60 minutes in oxygenated Krebs solution at 37° C or 24 to 28° C. (4) After the recovery period the rate of oxygen utilization was measured under resting conditions and under stimulation at 24 to 28° C or 37° C.

Measurement of oxygen utilization by the heart muscle strips was determined according to the modified method of Carlson and associates.[8,9] The muscle chamber was constructed of Lucite fitted with a muscle holder and perfused with Krebs solution at a flow rate of 1.5 ml. per hour. The electric current was recorded on a Northrup Speedomax with a chopper amplifier, a calomel half-cell and a platinum oxygen electrode. Measurements were made under resting conditions and under square wave stimulation (voltage was 10 to 15 per cent [range 5 to 50 mv.] above threshold for a duration of 1 to 2 msec. and a frequency of 1 per second). The isometric contractile tension was measured with an RCA 5734 transducer.

The oxygen electrodes were calibrated by measuring the potential in Krebs solution being maintained at saturation by bubbling 95 per cent oxygen/5 per cent carbon dioxide and at saturation by bubbling 60 per cent oxygen/5 per cent carbon dioxide/35 per cent nitrogen. The difference in potentials observed represents 35 per cent oxygen. Oxygen utilization by the muscles under rest and stimulation was calculated from the potential difference and expressed as milliliters of oxygen utilized per 100 grams of wet weight muscle per minute. Multiplying this value by 26.9 yielded the oxygen utilization data in μMGH units, i.e., micromoles oxygen per gram muscle per hour.

Results

The rate of oxygen utilization by human and rat atrial and ventricle muscle is reported in Table I. It may be seen that stimulation of the atrial muscles resulted in increased oxygen utilization. The anoxic stress at body temperature resulted in decreased oxygen utilization, whereas hypothermia protected the heart muscles from anoxic stress. A comparison of the oxygen utilization and contraction of the heart muscles is given in Table II. Again hypothermia protected the tissue from changes induced by anoxic stress. Most striking is the marked similarity of human and rat heart tissues under "normal" in vitro conditions, hypothermia and anoxic stress (Tables I and II). Typical tracings of heart contraction with and without hypothermia protection to anoxic stress are shown in Figs. 1, 2, and 3 for both human and rat heart muscle.

The data for the patients in this study were grouped according to severity of the heart defect. The results of this subclassification are presented in Tables III and IV.

Discussion

The advent of open heart surgery with the aid of extracorporeal support has made it possible to study viable human heart

*Calculation of the rate of oxygen utilization by heart muscle: $\Delta P = \Delta P$ (P Pa) [illegible] v_1 [illegible] $\Delta P_1 v_3$ [illegible] 60/100 [illegible] 24 v_2

[illegible] Δ = change in parameter noted; P = partial pressure oxygen in mm. Hg (T and P constant); Pa = per cent of oxygen present; 6 [illegible] 10^{-4} (T and P constant); P = vapor pressure of water (T and P constant); P = barometric pressure (T constant); v_1 = volume of oxygen utilized (T, P, t, and m constant); v_2 = volume of oxygen flow (T and P constant); [illegible] solubility of oxygen in Krebs solution (T and P constant); [illegible] = mass of tissue [illegible] oxygen utilized (T, P, t, and m constant).

The effect of hypothermia and anoxia upon oxygen consumption and contractility of human and rat heart muscle

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The heart is inadvertently subjected to varying periods of anoxic stress during open heart surgery with the aid of extracorporeal support[1-3] and hypothermia is often utilized as a protective measure because it has been shown to preserve the tolerance of the heart muscle to anoxic stress.[3,4,14]

The advent of open heart surgery has made available for the first time small bits of human heart muscle which are ordinarily discarded as part of the cannulation technique. These small bits of right atrial and right ventricular muscle were used to measure the protective effect of hypothermia after anoxic stress as reflected by oxygen utilization and the contraction response of the muscle strips. Although in vivo models as well as heart muscle from experimental animals have been the subject of investigation for a number of years, very few reports are available about the response of human heart muscle to hypothermia and anoxia in an in vitro system. The observations on the human heart muscle and parallel experiments with rat heart muscle strips are the subjects of this report.

Methods

Human heart muscle was obtained from patients at the time of open heart surgery. During cannulation small pieces of right atrial muscle were removed and normally would have been discarded. In the experiments reported in this paper these pieces of tissue were collected in cold (24 to 28° C.) oxygenated Krebs solution. Right

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The following abbreviations are used in Tables III and IV of this article:

AI, Aortic insufficiency
AVC, atrioventricularis communis
AVS, aortic valvar stenosis
IASD, interatrial septal defect (secundum)
IVSD, interventricular septal defect
MI, mitral insufficiency
MS, mitral stenosis
PDA, patent ductus arteriosus
RV, right ventricle
TF, tetralogy of Fallot
PVS, pulmonary valve stenosis

oxygen consumption data for atrial strips from patients and rats were in the same range under hypothermia and normothermia. This fact is surprising because one would expect the oxygen consumption to be lower under hypothermic conditions. This is certainly so in vivo[3,15-24] but the response described in the above study may be peculiar to the in vitro model which was used in these experiments. When the muscles were stimulated there was the expected increase in oxygen utilization. The oxygen consumption of both the rat left ventricular and human right ventricular samples was relatively higher than that of the left atrial strips.

Table II. Comparison of the rate of oxygen utilization and contraction heights in heart muscle after recovery from anoxic stress

Heart tissue	Recovery after anoxic stress			
	Normothermia (37 to 38° C.)		Hypothermia (4 to 27° C)	
	Oxygen utilization	Contraction height	Oxygen utilization	Contraction height
A. Atrial muscle	%	%	%	%
(1) Human	69	74	99	95
(2) Rat	66	66	123	103
B. Ventricle muscle				
(1) Rat	83	70	98	97

The experimental details are given in Methods and the footnote on p. 89 and the legend to Table I.

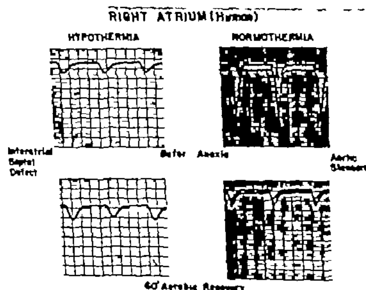


Fig. 1. Contraction of human atrial muscle before and after anoxic stress under normothermia and hypothermia. The experimental details are given in Methods.

tissue in *in vitro* systems. Heart muscle strips from both atrial and ventricular areas were studied using oxygen utilization and muscle contraction as indices of heart muscle functional integrity. These muscles were subjected to anoxic stress for 60 minutes as well as the protective action of hypothermia. Heart muscles from rats were studied in a manner to provide a comparison between the species and to relate the studies on human heart muscle to the literature which deals extensively with small animal heart physiology.

Oxygen consumption and contraction. The

*Table I. Rate of oxygen utilization by heart muscle**

	Normothermia (37 to 38° C.) (μMGH)		*Hypothermia (24 to 27° C.) (μMGH)*	
	Resting	*Stimulated*	*Resting*	*Stimulated*
A. *Atrial muscle*				
(1) Human				
Control	45.0 ± 4.0(21)	71.0 ± 7.0(13)	59.8 ± 3.8(32)	64.8 ± 10.0(10)
Recovery	25.2 ± 4.3(8)	48.6 ± 13.7(8)	45.9 ± 7.2(8)	74.1 ± 10.0(8)
% of control	56	69	72	114
(2) Rat				
Control	43.5 ± 3.0(26)	61.0 ± 5.6(16)	44.9 ± 2.8(32)	60.4 ± 6.2(8)
Recovery	29.0 ± 4.0(11)	44.0 ± 2.8(8)	42.2 ± 3.2(8)	60.5 ± 7.0(8)
% of control	67	72	94	100
B. *Ventricle muscle*				
(1) Human				
Control			69.3 ± 13.1(7)	
Recovery			63.0 ± 10.0(4)	
% of control			91	
(2) Rat				
Control	57.0 ± 5.9(27)	58.6 ± 6.1(16)	55.0 ± 2.8(40)	55.9 ± 7.3(15)
Recovery	45.0 ± 13.7(8)	53.2 ± 7.5(8)	60.2 ± 5.8(8)	72.5 ± 12.6(8)
% of control	79	91	109	130

*The experimental details are given in Methods and the footnote on p. 89. Recovery refers to muscle subjected to anoxic stress and then returned to the aerobic Krebs solution. Control refers to muscles not subjected to anoxic stress, but maintained in aerobic Krebs solution.

μMGH, Micromoles per gram tissue each hour ± standard deviation; the numbers in parentheses are the number of muscle strips utilized.

Statistical comparisons:

(1)	Human	Normothermia	Resting	Control	
	Rat	Normothermia	Resting	Control	N.S.
(2)	Human	Normothermia	Stimulated	Control	
	Rat	Normothermia	Stimulated	Control	N.S.
(3)	Human	Normothermia	Resting	Recovery	
	Rat	Normothermia	Resting	Recovery	N.S.
(4)	Human	Normothermia	Stimulated	Recovery	
	Rat	Normothermia	Stimulated	Recovery	N.S.
(5)	Human	Normothermia	Resting	Control	
	Human	Normothermia	Resting	Recovery	$p < 0.001$
(6)	Human	Normothermia	Stimulated	Control	
	Human	Normothermia	Stimulated	Recovery	< 0.005
(7)	Human	Hypothermia	Resting	Control	
	Human	Hypothermia	Resting	Recovery	$p < 0.001$
(8)	Human	Hypothermia	Stimulated	Control	
	Human	Hypothermia	Stimulated	Recovery	$p < 0.05$

oxygen consumption data for atrial strips from patients and rats were in the same range under hypothermia and normothermia. This fact is surprising because one would expect the oxygen consumption to be lower under hypothermic conditions. This is certainly so in vivo [4, 28] but the response described in the above study may be peculiar to the in vitro model which was used in these experiments. When the muscles were stimulated there was the expected increase in oxygen utilization. The oxygen consumption of both the rat left ventricular and human right ventricular samples was relatively higher than that of the left atrial strips.

Table II. Comparison of the rate of oxygen utilization and contraction heights in heart muscle after recovery from anoxic stress

Heart tissue	Recovery after anoxic stress			
	Normothermia (37 to 38° C.)		Hypothermia (24 to 27° C.)	
	Oxygen utilization	Contraction height	Oxygen utilization	Contraction height
A. Atrial muscle	%	%	%	%
(1) Human	69	74	99	95
(2) Rat	66	66	123	103
B. Ventricle muscle				
(1) Rat	83	70	98	97

The experimental details are given in Methods and the footnote on p. 89 and the legend to Table I.

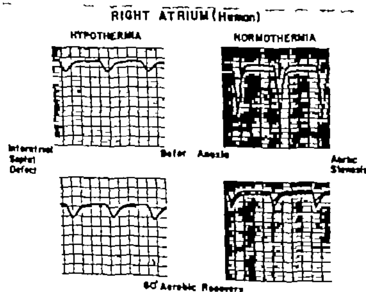


Fig. 3. Contraction of human atrial muscle before and after anoxic stress under normothermia and hypothermia. The experimental details are given in Methods.

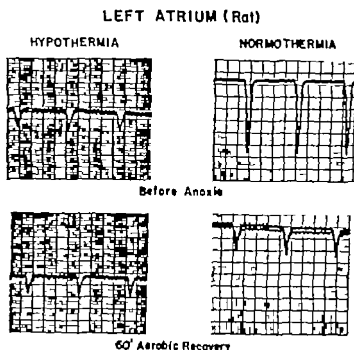


Fig 2 Contraction of rat atrial muscle before and after anoxic stress under normothermia and hypothermia. The experimental details are given in Methods.

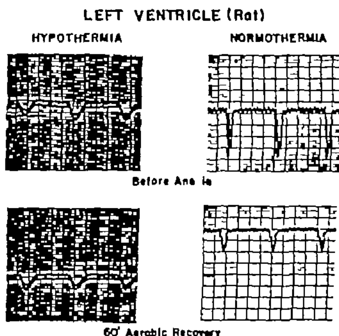


Fig 3 Contractions of rat ventricle muscle before and after anoxic stress under normothermia and hypothermia. The experimental details are given in Methods.

This is probably a reflection of greater tension development and more energy utilization by the stronger ventricular muscle.

There is little doubt that moderate hypothermia has a striking effect in preserving oxygen utilization by heart muscle[17] as well as the mechanical strength (contraction) of the muscle It is of interest that the recovery of the oxygen consumption ability was better in the muscle strips which were stimulated and this is probably

*Table III. Rate of oxygen utilization by human atrial muscle from patients with heart defects**

Heart defect	*Relative severity of defect( )*	*Normothermia (37 to 38° C.) (μl/GH)*	*Hypothermia (24 to 27° C.) (μl/GH)*
IASD	+	44.3 ± 5.9(8)	63.2 ± 8.3(8)
IVSD	++		51.3 ± 5.6(4)
Tetralogy of Fallot	+++		44.2 ± 6.2(8)
Combined defects	++++	37.1 ± 6.2(8)†	40.0 ± 6.5(7)‡

*Experimental details are given in Methods and the footnote on p. 89 and the legend to Table I. These data refer to nonstimulated muscle strips. See below for statistical comparisons.

† VS + PDA, PDA + IVSD + AS (subaortic stenosis + endocardial fibroelastosis (left ventricle)), corrected transposition, coarctation of the aorta + AVS + endocardial fibroelastosis (left ventricle), MI + MS; IASD (anomalous [illegible]) + MI, IASD + PVS.

‡IVSD + AI, subacute bacterial endocarditis, MI + MS, MS (congestive heart failure), AVC; IVSD + PDA (2), MI (congestive heart failure).

Statistical comparisons:

(1)	IASD	Hypothermia	
	IVSD	Hypothermia	.01
(2)	IVSD	Hypothermia	
	Tetralogy	Hypothermia	> .05
(3)	Tetralogy	Hypothermia	
	Combined	Hypothermia	> 0.3

a reflection of a relatively more "normal" physiologic state of the muscle, i.e., approaching the in vivo state. Hypothermia had a protective effect on the mechanical activity of heart muscle in that the contraction height returned almost to the base line in muscle which had been subjected to anoxic stress under hypothermia, but this was not so under normothermic conditions.[25] (Tables I through IV, Figs. 1 to 3.)

It is well recognized that patients with a combination of congenital cardiac malformations or those with severe acquired heart disease in failure are in the high risk group when they undergo surgery with the aid of extracorporeal support. It is of interest to focus on the results which show that when the right atrial strips from patients were divided into four categories of increasing severity of heart disease, the strips showed significant differences in oxygen utilization. The right atrial strips from patients with interatrial septal defects (these patients are usually asymptomatic) showed the highest oxygen consumption values. In contrast, the right atrial strips from patients who were symptomatic, i.e., those in congestive heart failure and those with a combination of serious congenital heart malformations, showed the lowest oxygen consumption values.

The recovery of oxygen consumption after anoxic stress under hypothermia and normothermia was also studied in atrial strips from patients with atrial septal defects, and those from patients with more serious congenital or acquired heart disease. There was no significant difference in recovery under hypothermia in the two groups while at rest or when stimulated. However, under normothermia the recovery of oxygen utilization was significantly higher in the group with the more serious heart disease. This is surprising and may possibly be explained by the fact that the heart muscle from the patients with the more serious heart disease may be better accommodated to work in a relatively anoxic state when compared with heart muscle strips from the asymptomatic patients with interatrial septal defects. The number of samples was small and therefore this observation must be examined again with more patients (Tables III and IV).

Summary

The advent of open-heart surgery has made available for the first time small bits of human heart muscle which are ordinarily discarded as part of the cannulation technique. These small bits of right atrial muscle and right ventricular muscle were

*Table IV Recovery of rate of oxygen utilization by human atrial muscle for patients with heart defects after 60 minutes of anoxia**

Defect	Oxygen consumption after recovery period	
	Normothermia (% control)	Hypothermia (% control)
I IASD		
Resting	58 ± 6 3(5)	95 ± 4 4(4)
Stimulated	59 ± 9 4(4)	99 ± 13 6(4)
II Other defects		
Resting	95 ± 10 7†(4)	89 ± 12 4(3)§
Stimulated	74 ± 11 9‡(3)	102 ± 6 1(4)‖

*Experimental details are given in Methods and the footnote on p. 89 and the legend to Table I. See below for statistical comparisons.

†AVS + PDA; PDA + IVSD + AS subaortic stenosis + endocardial fibroelastosis (left ventricle); corrected transposition.

‡MI + MS; MS; IASD + PVR.

§MS TF AVC.

‖TF MI TF; t chambered RV IVSD

Statistical comparisons

(1)	IASD	Normothermia	Resting	
	IASD	Hypothermia	Resting	$p < 0.001$
(2)	IASD	Normothermia	Resting	
	Other defect	Normothermia	Resting	$p < 0.001$
(3)	Other defects	Normothermia	Resting	
	Other defect	Hypothermia	Resting	$p < 0.001$
(4)	Other defects	Normothermia	Stimulated	
	Other defects	Hypothermia	Stimulated	$p < 0.01$
(5)	IASD	Normothermia	Stimulated	
	Other defects	Normothermia	Stimulated	$p > 0.1$
(6)	IASD	Hypothermia	Resting	
	Other defects	Hypothermia	Resting	$p > 0.4$
(7)	IASD	Hypothermia	Stimulated	
	Other defects	Hypothermia	Stimulated	$p > 0.7$

used to measure the protective effects of hypothermia after anoxic stress as reflected by the contraction response and oxygen utilization of the muscle strips. Although *in vivo* models as well as heart muscle from experimental animals have been the subject of investigation for a number of years very few reports are available about the response of human heart muscle to hypothermia and anoxia in an in vitro system The results of the experiments in this study which also included parallel experiments using rat left atrial and ventricular muscle show that hypothermia exerts a very dramatic protective effect on heart muscle subjected to anoxic stress by preserving contractile power and oxygen consumption

The authors acknowledge, with appreciation, the help of Dr George Noren of the University of Minnesota Medical School during his tenure as a Fellow of the Hartford Foundation at the St Louis Children s Hospital in the initial phase of this work.

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*Experimental detail re given in Methods and the footnot on p. 89 and the legend t Table I See below for statistical comparisons.
†AVB + PDA; PDA + IVSD + AS; subaortic stenosis + endocardial fibroelastosis (left ventricle) corrected transposition.
‡MI + MS; MS; IASD + PVS.
§MS; TF; AVC.
‖TF; MI; TF; tw chambered RV IVSD.

Statistical comparisons

(1)	IASD	Normothermia	Resting	
	IASD	Hypothermia	Resting	$p < 0.001$
(2)	IASD	Normothermia	Resting	
	Other defect	Normothermia	Resting	$p < 0.001$
(3)	Other defects	Normothermia	Resting	
	Other defect	Hypothermia	Resting	$p < 0.001$
(4)	Other defects	Normothermia	Stimulated	
	Other defects	Hypothermia	Stimulated	$p < 0.01$
(5)	IASD	Normothermia	Stimulated	
	Other defects	Normothermia	Stimulated	$p > 0.1$
(6)	IASD	Hypothermia	Resting	
	Other defect	Hypothermia	Resting	$p > 0.4$
(7)	IASD	Hypothermia	Stimulated	
	Other defects	Hypothermia	Stimulated	$p > 0.7$

used to measure the protective effects of hypothermia after anoxic stress as reflected by the contraction response and oxygen utilization of the muscle strips. Although *in vivo* models as well as heart muscle from experimental animals have been the subject of investigation for a number of years very few reports are available about the response of human heart muscle to hypothermia and anoxia in an in vitro system The results of the experiments in this study which also included parallel experiments using rat left atrial and ventricular muscle show that hypothermia exerts a very dramatic protective effect on heart muscle subjected to anoxic stress by preserving contractile power and oxygen consumption

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gauge needle connected by polyethylene tubing to a microsyringe. The presence of this needle had no effect on either mean or instantaneous flow. Supplementary anesthetic and pharmacologic blocking agents were injected through a catheter in the jugular vein.

A Walton-Brodie strain-gauge arch was sutured on a portion of myocardium within the area of distribution of the anterior descending coronary artery so that changes in contractile force produced by nicotine could be determined at the same time as the coronary flow changes. In two dogs an additional strain gauge was placed in a zone of myocardium in the distribution of the anterior descending coronary artery but upstream from the point of injection of the drug.

The parameters measured were registered on a Beckman S II Dynograph recorder. The drugs used were norepinephrine bitartrate (Levophed, Winthrop), nicotine acid tartrate (K and K Laboratories), propranolol hydrochloride (Ayerst Laboratories, Inc.), and pentolinium tartrate (Wyeth). Doses are referred to in terms of salt except for norepinephrine which is referred to in terms of base.

Diastolic and systolic coronary blood flow were calculated by planimetry of the appropriate area under the flow curve. Diastole was considered to start with the inflection in the flow trace coincident with the closure of the aortic valves and marked by the incisura of the aortic pressure record. Systole was considered to begin with the onset of coronary flow deceleration immediately preceding the systolic upstroke of the pressure curve. All measurements were averaged over three cycles.

Results

The mean control values and the standard deviations for coronary flow, arterial pressure and heart rate in the ten dogs were as follows:

Systolic arterial pressure	122 ± 22 mm. Hg
Diastolic arterial pressure	87 ± 16 mm. Hg
Heart rate	185 ± 22 beats per min.
Duration of systole	166 ± 22 msec
Duration of diastole	139 ± 27 msec
Stroke systolic coronary flow	0.029 ± 0.018 ml.
Stroke diastolic coronary flow	0.065 ± 0.022 ml.
Total stroke coronary flow	0.091 ± 0.047 ml.

Effects of intracoronary nicotine. The threshold dose was the same for both the coronary flow and myocardial contractile force responses in each animal and varied from one to 10 μg. Maximal effects occurred with 80 to 100 μg. Effective doses increased contractile force and reduced the duration of myocardial contraction and the time to peak tension. These changes appeared to occur only downstream from the site of injection since no changes were registered by an additional strain gauge arch upstream from this point. This apparent localization of the response to a relatively small portion of the myocardium probably accounts for the fact that changes in aortic pressure were not observed except with doses above 50 μg. Heart rate was unchanged but the duration of systole of the myocardium downstream from the injection site was reduced (mean reduction 20 per cent, standard deviation 10 per cent) and the duration of "diastole" was correspondingly increased. Total stroke systolic coronary flow and systolic flow per millisecond systole were reduced and total stroke diastolic coronary flow and diastolic coronary flow per millisecond were increased. Total stroke coronary flow increased and end-diastolic coronary vascular resistance diminished. All these changes began within 4 seconds of injection, reached a maximum 4 to 8 seconds later and returned to normal within 3 minutes.

The over all effects of increasing doses of nicotine are shown at slow paper speed in Fig. 1 and the details of the instantaneous coronary flow and contractile force changes are seen at rapid paper speed in Fig. 2. The changes produced by the intracoronary injection of 20 μg of nicotine in all ten animals are shown in Fig. 3.

The effects of nicotine on coronary flow and myocardial contraction were compared with those of norepinephrine in four of the ten dogs. The responses to both agents were very similar (Fig. 4) and were blocked by intravenous propranolol, 1 mg. per kilogram (Fig. 5). The nicotine responses were also blocked by intravenous pentolinium 0.5 mg. per kilogram in each of another four animals (Fig. 6). Note that both propranolol and pentolinium produced considerable depression of contractile force presumably because of the high degree of sympathetic tone exhibited by open-chest

The effect of nicotine on the coronary circulation of dogs

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*Marta I Blesa***
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Although the effects of nicotine on coronary blood flow have been extensively investigated most of the studies have been concerned with average flow determinations and with coronary venous outflow rather than coronary arterial inflow The present study reports the action of nicotine on instantaneous coronary arterial flow in anesthetized dogs Instantaneous coronary flow measurements provide much more information than average flow and permit a better assessment of some of the important determinants of coronary flow which might be altered by the drug e g extravascular compression relative duration of systole and diastole and end-diastolic vascular resistance.[1,2] In order to avoid the complex systemic actions of nicotine injections were made directly into the coronary arterial system in doses insufficient to produce systemic responses. Because of the reported liberation of catecholamines in the heart by nicotine[3] the effects of this drug were examined before and after the induction of beta adrenergic blockade with propranolol

Methods

A total of ten dogs weighing 10 to 18 kilograms were anesthetized with intravenous pentobarbital sodium 40 mg per kilogram and intubated The chest was opened in the fifth left intercostal space while ventilation was maintained with a Bird Mark 8 respirator After incising the pericardium the anterior descending branch of the left coronary artery was carefully dissected over a distance of approximately 1 cm and a noncannulating flow probe was placed on the vessel Flow was determined by means of a Biotronex BL-610 flowmeter The zero reference point was frequently determined during each experiment by mechanically occluding the vessel distal to its probe Calibration was performed by placing the probe on a branch of the femoral artery and withdrawing a known amount of blood from this vessel at rates from 5 to 80 ml per minute with a Harvard infusion withdrawal pump

Aortic pressure was determined with a Statham P23Db transducer via a polyethylene tube (PE200) approximately twelve artery inches long inserted into the carotid and advanced into the arch of the aorta The frequency response of both the flow and pressure measuring systems was 25 Hz (−3 db)

Drugs were injected directly into the coronary artery through an indwelling 30

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*This ork was done during the tenure of an Established Investigatorship of the American Heart Association. Reprint requests t Dr Gordon Ross, Department of Physiology U.C.L A. School of Medicine, Los Angeles, Calif. 90024
**Postdoctoral Trainee supported by United States Public Health Service Training Grant No. 5 T1 HE 5696.

200
150
100
50
0
-50
PERCENT CHANGE
Stroke Systolic
Systolic Flow per msec
Stroke Diastolic Flow
Diastolic Flow per msec
Stroke Flow
EDVR
Contractile Force

Fig. 3. Mean per cent changes ± standard deviations produced by 20 μg of intracoronary nicotine in ten dogs. The numerical values were as follows: stroke systolic coronary flow −55 ± 24 per cent; systolic coronary flow per millisecond, −37 ± 26 per cent; stroke diastolic coronary flow +62 ± 24 per cent; diastolic coronary flow per millisecond, +42 ± 35 per cent; total stroke coronary flow +32 ± 21 per cent; end-diastolic vascular resistance, −22 ± 13 per cent; contractile force, +132 ± 63 per cent.

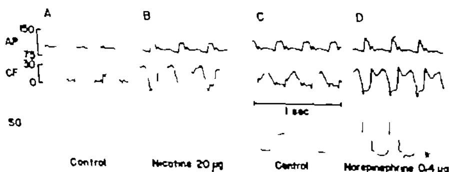


Fig. 4. Similarity of instantaneous coronary flow (*CF*) and contractile force (*SG*) changes produced by intracoronary nicotine and intracoronary norepinephrine. *A*, Control. *B*, Eight seconds after intracoronary nicotine 20 μg. *C*, Control. *D*, Eight seconds after 0.4 μg of intracoronary norepinephrine.

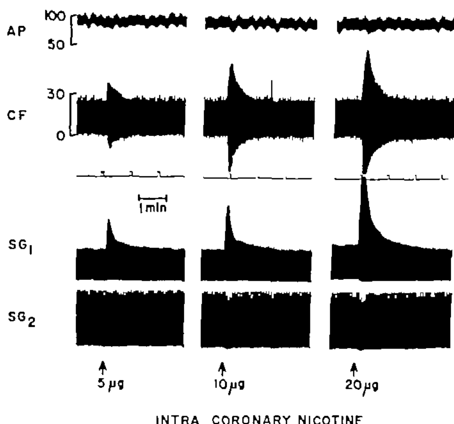


Fig 1 Effect of increasing doses of intracoronary nicotine on arterial pressure (AP), instantaneous anterior descending coronary artery flow (CF) and contractile force of segment of myocardium downstream (SG_1) and upstream (SG_2) from the point of nicotine injection In this, and all subsequent figures pressures are measured in millimeters of Hg and flows in milliliters per minute.

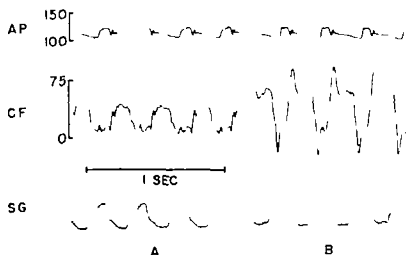


Fig 2 Effect of intracoronary nicotine on arterial pressure (AP), instantaneous coronary flow (CF), and myocardial contractile force (SG). A Pre-injection record. B Eight seconds after 20 μg intracoronary nicotine.

PERCENT CHANGE

200
150
100
50
0
-50

St oke Systolic

Systolic Flow per msec

Stroke Diastolic Flow

Diastolic Flow per msec

St oke Flow

EDVR

Contractile Force

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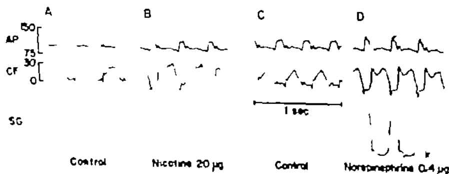


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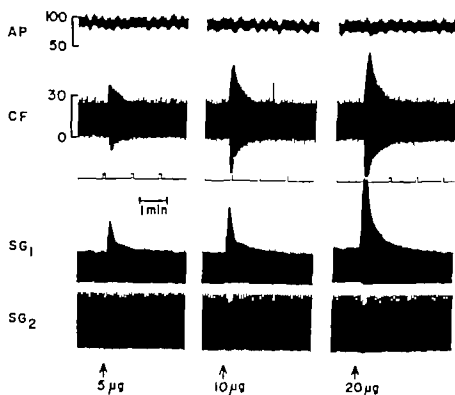


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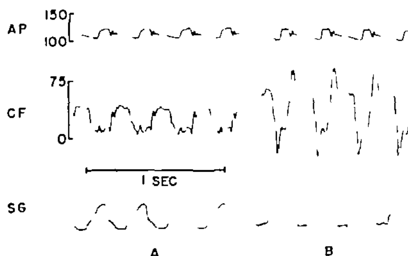


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neous increased force of myocardial contraction and an increase in coronary flow These changes began within 4 seconds of injection, i.e., before the drug could have reached the systemic circulation and were unaccompanied by changes in heart rate and arterial pressure or by changes in myocardial force upstream from the point of injection. Examination of the instantaneous coronary flow records showed that the increased coronary flow was partly due to coronary vasodilatation as shown by the reduced end-diastolic vascular resistance and partly to an increase in the duration of diastole during which most of the coronary inflow takes place. Systolic flow was reduced and even reversed All the coronary flow changes, which were blocked by propranolol, were strikingly similar to those produced by norepinephrine (see Fig 4) and by sympathetic nerve stimulation[9] and were blocked by propranolol This suggests that the effects of nicotine on the myocardium and on coronary flow are mediated by catecholamines. This view is supported by previous studies which have shown that propranolol blocks the tachycardia induced by the injection of nicotine into the sinus node artery in dogs[10] and the increased cardiac output and rise in arterial pressure produced by intravenous nicotine in cats.[11] Pretreatment with reserpine also blocks the coronary flow increase produced by nicotine *in the isolated cat heart*[12] and inhibits the chronotropic effect of nicotine in the isolated rabbit atrium

The rapid onset of the inotropic response to nicotine in our experiments and its apparent localization to the area downstream from the point of injection indicate that any catecholamine release or potentiation must have occurred from sites *within* the ventricular myocardium Chromaffin cells have been described in the atria of dogs[13] but not in the ventricle. It therefore seems likely that nicotine released norepinephrine from adrenergic nerve terminals *within the* muscle. The coronary flow changes we observed may have been entirely secondary to the metabolic and mechanical effects of myocardial stimulation. Certainly we never saw any alteration of coronary flow in the absence of an inotropic response and when the latter was blocked by propranolol nicotine had no effect on coronary flow On the other hand it is possible that norepinephrine was liberated simultaneously in the coronary resistance vessels and in the myocardium Studies of the effects of nicotine on isolated small coronary vessels would be helpful in clarifying this point.

Our results have confirmed previous observations that the cardiac effects of nicotine are prevented by pretreatment with ganglionic blocking agents.[11] As far as we are aware adrenergic ganglion cells have never been described in the canine ventricle. The nicotine-blocking effect of pentolinium in our experiments must therefore have occurred at a nonganglionic site. During recent years, the cholinergic link hypothesis of adrenergic transmission has excited much interest.[16] According to this hypothesis, the action potential passing down the postganglionic sympathetic nerve fiber causes the release of acetylcholine which in turn releases norepinephrine. Hexamethonium and pentolinium have been found to block the adrenergic effect of acetylcholine but not that of sympathetic nerve stimulation.[6] Burn and Gibbons[17] have suggested that certain ganglionic blocking agents might block the sympathomimetic effects of acetylcholine by preventing the entry of acetylcholine into the postganglionic fiber Nicotine, like acetylcholine, can produce adrenergic effects in many organs.[18] It is therefore conceivable that nicotine enters postganglionic fibers within the myocardium and causes the release of norepinephrine by an action involving the cholinergic link mechanism. Pentolinium by preventing the entry of nicotine into the fiber would therefore block its sympathomimetic effects. These ideas concerning the interaction of nicotine and pentolinium at the cardiac sympathetic postganglionic nerve terminals are admittedly speculative but they are put forward since it should be possible to test them One obvious approach would be to study the uptake of labelled nicotine by nerve fibers before and after pentolinium.

The authors wish to acknowledge the able technical assistance of Miss Madeline Kurrasch

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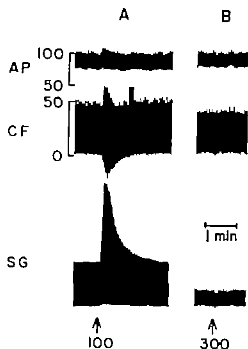


Fig 5 Blockade of coronary and myocardial responses to nicotine by propranolol. *A* Effects of intracoronary nicotine, 100 μg on arterial pressure (*AP*) instantaneous coronary flow (*CF*) and myocardial contractile force (*SG*) *B* Effects after intravenous propranolol 1 mg per kilogram. Note that 300 μg of intracoronary nicotine produced no response.

dogs anesthetized with pentobarbital. The effects of nicotine were not affected by atropine 1 mg per kilogram or vagotomy in any of the ten animals.

Discussion

An evaluation of the voluminous literature on the effects of nicotine on coronary flow is difficult because of the variety of species used and the differences in doses and routes of administration. The many studies with intravenous nicotine are particularly difficult to interpret because of the complex pharmacological effects of this agent which has been shown to stimulate and inhibit autonomic ganglia [4] to liberate catecholamines from the adrenal medulla,[5] to elicit axon reflexes and to have direct effects on vessels.[6] An added difficulty has been that until recently there has been no direct method of measuring rapid coronary flow changes. Most of the published reports indicate that nicotine increases coronary flow[7] although some earlier investigators found only a flow reduction.[7]

The present study showed that intracoronary nicotine in doses that produce no systemic effects and that do not elicit the Bezold Jarisch reflex produce a simulta

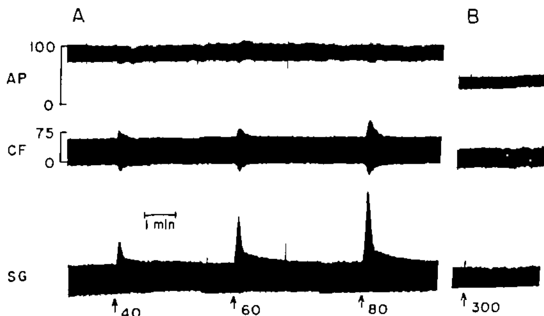


Fig 6 Effects of intracoronary nicotine on arterial pressure (*AP*) coronary flow (*CF*) and contractile force (*SG*). *A* Before pentolinium. *B* After intravenous pentolinium 0.5 mg per kilogram. Before pentolinium the responses to 40 60 and 80 μg of nicotine are shown. After pentolinium these doses were without effect and even increasing the dose to 300 μg failed to produce a response.

neous increased force of myocardial contraction and an increase in coronary flow. These changes began within 4 seconds of injection, i.e. before the drug could have reached the systemic circulation, and were unaccompanied by changes in heart rate and arterial pressure or by changes in myocardial force upstream from the point of injection. Examination of the instantaneous coronary flow records showed that the increased coronary flow was partly due to coronary vasodilatation as shown by the reduced end-diastolic vascular resistance and partly to an increase in the duration of diastole during which most of the coronary inflow takes place. Systolic flow was reduced and even reversed. All the coronary flow changes, which were blocked by propranolol, were strikingly similar to those produced by norepinephrine[8] (see Fig. 4) and by sympathetic nerve stimulation and were blocked by propranolol. This suggests that the effects of nicotine on the myocardium and on coronary flow are mediated by catecholamines. This view is supported by previous studies which have shown that propranolol blocks the tachycardia induced by the injection of nicotine into the sinus node artery in dogs[19] and the increased cardiac output and rise in arterial pressure produced by intravenous nicotine in cats.[11] Pretreatment with reserpine also blocks the coronary flow increase produced by nicotine in the isolated cat heart[20] and inhibits the chronotropic effect of nicotine in the isolated rabbit atrium.

The rapid onset of the inotropic response to nicotine in our experiments and its apparent localization to the area downstream from the point of injection indicate that any catecholamine release or potentiation must have occurred from sites within the ventricular myocardium. Chromaffin cells have been described in the atria of dogs[13] but not in the ventricle. It therefore seems likely that nicotine released norepinephrine from adrenergic nerve terminals within the muscle. The coronary flow changes we observed may have been entirely secondary to the metabolic and mechanical effects of myocardial stimulation. Certainly we never saw any alteration of coronary flow in the absence of an inotropic response and when the latter was blocked by propranolol nicotine had no effect on coronary flow. On the other hand it is possible that norepinephrine was liberated simultaneously in the coronary resistance vessels and in the myocardium. Studies of the effects of nicotine on isolated small coronary vessels would be helpful in clarifying this point.

Our results have confirmed previous observations that the cardiac effects of nicotine are prevented by pretreatment with ganglionic blocking agents.[14] As far as we are aware adrenergic ganglion cells have never been described in the canine ventricle. The nicotine-blocking effect of pentolinium in our experiments must therefore have occurred at a nonganglionic site. During recent years, the cholinergic link hypothesis of adrenergic transmission has excited much interest.[15] According to this hypothesis, the action potential passing down the postganglionic sympathetic nerve fiber causes the release of acetylcholine which in turn releases norepinephrine. Hexamethonium and pentolinium have been found to block the adrenergic effect of acetylcholine but not that of sympathetic nerve stimulation. Burn and Gibbons[17] have suggested that certain ganglionic blocking agents might block the sympathomimetic effects of acetylcholine by preventing the entry of acetylcholine into the postganglionic fiber. Nicotine, like acetylcholine, can produce adrenergic effects in many organs.[22] It is therefore conceivable that nicotine enters postganglionic fibers within the myocardium and causes the release of norepinephrine by an action involving the "cholinergic link" mechanism. Pentolinium by preventing the entry of nicotine into the fiber would therefore block its sympathomimetic effects. These ideas concerning the interaction of nicotine and pentolinium at the cardiac sympathetic postganglionic nerve terminals are admittedly speculative but they are put forward since it should be possible to test them. One obvious approach would be to study the uptake of labelled nicotine by nerve fibers before and after pentolinium.

The authors wish to acknowledge the able technical assistance of Miss Madeline Korrasch.

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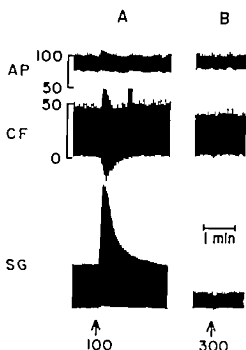


Fig 5 Blockade of coronary and myocardial responses to nicotine by propranolol 1 Effects of intracoronary nicotine 100 µg on arterial pressure (*AP*) instantaneous coronary flow (*CF*) and myocardial contractile force (*SG*) *B* Effects after intravenous propranolol, 1 mg per kilogram. Note that 300 µg of intracoronary nicotine produced no response

dogs anesthetized with pentobarbital. The effects of nicotine were not affected by atropine 1 mg per kilogram or vagotomy in any of the ten animals.

Discussion

An evaluation of the voluminous literature on the effects of nicotine on coronary flow is difficult because of the variety of species used and the differences in doses and routes of administration. The many studies with intravenous nicotine are particularly difficult to interpret because of the complex pharmacological effects of this agent which has been shown to stimulate and inhibit autonomic ganglia [4] to liberate catecholamines from the adrenal medulla,[5] to elicit axon reflexes and to have direct effects on vessels.[6] An added difficulty has been that until recently there has been no direct method of measuring rapid coronary flow changes Most of the published reports indicate that nicotine increases coronary flow [7] although some earlier investigations found only a flow reduction [7]

The present study showed that intracoronary nicotine in doses that produce no systemic effects and that do not elicit the Bezold Jarisch reflex produce a simulta

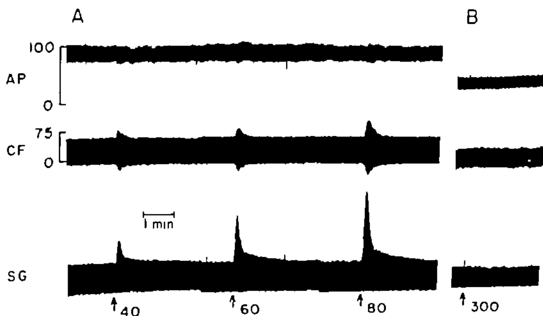


Fig 6 Effects of intracoronary nicotine on arterial pressure (*AP*) coronary flow (*CF*) and contractile force (*SG*) *A* Before pentolinium. *B* After intravenous pentolinium, 0.5 mg per kilogram. Before pentolinium the responses to 40, 60 and 80 µg of nicotine are shown. After pentolinium these doses were without effect, and even increasing the dose to 300 µg failed to produce a response

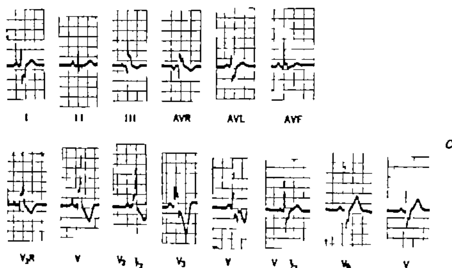


Fig. 1 cont'd For legend see opposite page

A

B

P.C. (no. 112-32-21) 6 yr. old ♀

P.C. (no. 112-32-21) 8 yr. old ♀

P.C. (no. 112-32-21) 7 wk. P.O.

C

Fig. A, Chest x-ray at age six. Heart size interpreted as within normal limits. B, At age 8, the heart size has increased markedly. C, Seven weeks after excision of fibromuscular diaphragm from the right ventricular outflow tract, the heart is distinctly smaller.

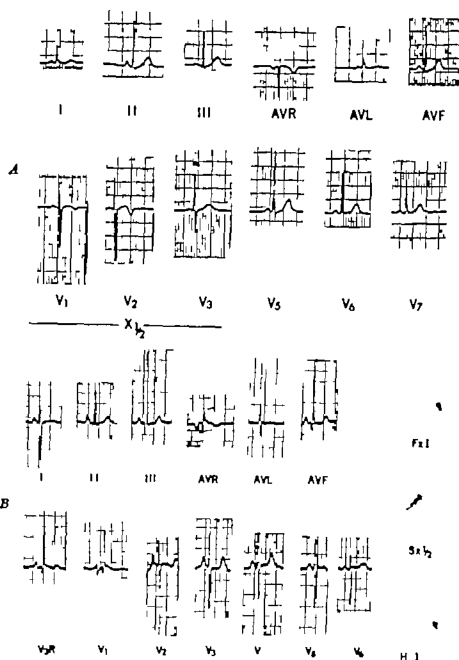


Fig 1 *A* Normal electrocardiogram at six years of age *B* At age eight, electrocardiogram demonstrates tall peaked P waves in Leads II and V . There was a 17 mm R wave in Lead V without an S wave The comparable voltages in V are 7 mm. R and 16 mm. S. There is a 2 5 mm. q wave in Lead V The interpretation is right axis deviation, right atrial hypertrophy right ventricular hypertrophy The vectorcardiogram confirms this impression indicating that the initial forces were to the left and posterior The P vector was larger than the T vector and pointed anteriorly *C* Seven weeks after excision of fibromuscular diaphragm from the right ventricular outflow tract. There was no change in the P waves, but the T waves have inverted in the right precordial leads. The prolonged QRS indicates bundle branch block after ventriculotomy

normal limits. No ejection clicks were heard. A thrill was noted along the lower left sternal border A Grade IV/VI harsh-to-blowing holosystolic murmur was heard loudest along the left sternal border radiating to base and apex as well as to the back. A Grade I/VI early decrescendo high-pitched diastolic murmur was heard along the left sternal border at the third to fourth intercostal space. A Grade I II/VI middiastolic rumble was heard at the apex and along the left sternal border The electrocardiogram showed a marked increase in right ventricular forces (Fig 1 *B*) Complete skeletal series was normal except for calcification of the nucleus pulposis of T_{4-5}. Chest x ray showed a marked increase in cardiac size (Fig 2 *B*). Liver function tests were within normal limits. Central venous pressure (brachiocephalic vein) was 150 mm. H_2O The circulation time was 30 seconds. A liver and heart scan were normal There was a normal excretory urogram.



Fig. 4. Section through the fibromuscular diaphragm of the right ventricular outflow tract, illustrating the thickened endocardial layer which in some places invades the margin of the otherwise normal appearing underlying myocardium. Fibroblasts are interspersed with predominantly collagen fibers, though Verhoeff stain reveals some elastic fibers in localized areas of the intimal thickening. (Hematoxylin and eosin ×150.)

ring-shaped mass of dense white fibrous tissue encircled the superior and inferior venae cavae. A second larger ring of tumor occupied the arteriovenous sulcus merging with atrial muscle on one side and ventricular muscle on the other. This second mass was connected near the mitral valve ring with the third tumor which encircled the pulmonary artery and aorta like a collar being 7.5 cm. in outside diameter and 2.5 to 4 cm. in width. Sections of these extrinsic masses disclosed a mixture of subepicardial fat and edematous nerve trunks. The concentrically arranged fibrils of the latter extended into the myocardium where they were interspersed between the muscle bundles. There was, in addition, proliferation of fibrous connective tissue presumably limited to the fibrous collars, though the exact location was not stated, nor was the endocardial surface described. Since the child had not had a cardiac catheterization, the hemodynamic effects of the obstruction which resulted from these tumors cannot be evaluated. The only similarity between this case and ours is that fibrous tissue infiltrated the myocardium. In Pung's case this was probably limited to the epicardial layer whereas in our case it occurred at the endocardial surface.

In addition to obstruction invasive tumors may change the compliance of heart muscle, and affect valve function, conduction of the electrical impulse and eventually coronary circulation. In Pung's case some or all of these effects may have been present. In our case change in compliance, if present, probably resulted from dilation of the right ventricular chamber proximal to the obstruction causing tricuspid valve malfunction. Though some of the conductive tissue was undoubtedly involved in the fibrotic endocardial lesion, conduction delay did not appear until after surgery (Fig. 1, C) when the effects could be attributed to ventriculotomy. Angiographic and surgical observation indicate that the crista supraventricularis was not involved in the fibromuscular diaphragm. The lesion was therefore either superimposed on an anomalous muscle bundle of the right ventricle or on an otherwise inconspicuous muscle of the

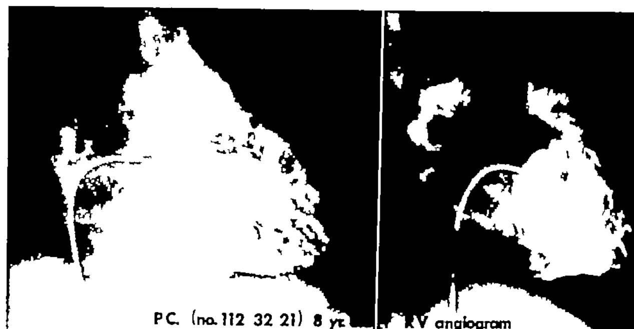


Fig 3 Right ventricular biplane angiograms demonstrating the obstructive lesion of the right ventricular outflow tract with normal appearing infundibular cavity and pulmonic valve beyond There is marked hypertrophy of the right ventricular musculature.

Her diagnosis before cardiac catheterization was pulmonary stenosis due to aberrant muscle band or tumor The femoral vein and artery were entered percutaneously Right atrial (= 14 v = 8) and right ventricular (117/6/15 mm Hg) pressures were elevated The right ventricular infundibulum where the pressure was 21/3 mm Hg was entered with difficulty The pulmonary artery pressure was 21/10 mm Hg No shunting was noted by either dye curves oximetry or cineangiograms. A biplane angiocardiogram of the right ventricle revealed a discrete obstruction to the right ventricular outflow tract (Fig 3)

At open-heart surgery no tumor mass was noted on gross inspection of the heart. Enlargement of the venae cavae was marked The right atrium was distended The pulmonary artery was of normal size. Coronary artery distribution was normal The hypertrophied outflow tract was incised under cardiopulmonary bypass The infundibular chamber was noted to be widely dilated the distal aspect leading to a normal annulus and valve There was only one communication between the infundibulum and the right ventricular chamber a 2 to 2.5 m fenestration within a white fibrous diaphragm which blended with the muscle of the hypertrophied infundibulum and led to the main right ventricular cavity which though dilated showed normal tricuspid attachments. Numerous coronary branches led to this diaphragm which was excised. Following excision right ventricular and pulmonary artery systolic pressures were essentially equal Right ventricular failure steadily decreased postoperatively with the aid of diuretics, digitalis, and a low salt diet. On the nineteenth postoperative day no murmurs were heard and the liver was noted 3 cm. below the right costal margin Heart sounds were within normal limits. A chest x-ray demonstrated decrease over all heart size (Fig 2, C). The electrocardiogram showed a marked decrease in right ventricular hypertrophy (Fig 1 C).

The excised specimen showed a 1 to 2 mm white fibrous thickening of the endocardium which on microscopic section revealed extensive proliferation of elastic and collagen fibers (Fig 4)

Discussion

Cardiovascular involvement in von Recklinghausen's disease is uncommon The most frequently reported anomalies are stenotic lesions of the renal arteries causing hypertension[1-4] often associated with coarctation of the abdominal aorta[3] Histologically previously described lesions resemble neurofibromata of the adventitia which constrict the lumina of the involved segments of the vessel Though intimal thickening is also described in these cases, it is unclear whether this is due in some cases to primary invasion by the neurocutaneous lesions or a secondary effect of the adventitial lesion Excision and vessel reconstruction has resulted in reversion of blood pressure to normal limits[4] but long term improvement resulted only when nephrectomy was performed[1]

In 1955 Pung and Hirsch[7] reported a case of neurofibromatosis of the heart in a 3-year-old girl The heart was hypertrophied and misshapen at autopsy A

Effect of heart rate on hemodynamics in mitral stenosis

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The relationship between the diastolic filling period and the diastolic gradient across the mitral valve in the presence of mitral stenosis is well known. An increase in pulmonary artery wedge pressure has been demonstrated in patients with mitral stenosis and atrial fibrillation by increasing the heart rate by artificial ventricular pacing.[1] The patient to be discussed below presented the unusual combination of significant mitral stenosis and atrial fibrillation with complete atrioventricular block. This combination of findings afforded the opportunity to examine the effect of changes in the diastolic filling period on the mitral diastolic pressure gradient over a rate range of 32 to 150 per minute.

Case report

This 75-year-old Caucasian married male was admitted to the Salt Lake City Veterans Administration Hospital on Nov. 15, 1967, because of exertional dyspnea and fatigue. The patient was told he had a heart murmur and was given a medical discharge from the military service during World War I following an attack of acute rheumatic fever.

He had no cardiorespiratory symptoms until 1940 when he began having left anterior chest pain usually related to exertion and relieved by rest. In 1960 he noted the onset of progressive exertional dyspnea, easy fatigability, intermittent pedal edema, and orthopnea.

He was admitted to this hospital for the first time in 1963 because of urinary bladder calculus, at which time he was noted to have a Grade III/VI apical holosystolic murmur. An electrocardiogram was interpreted to show atrial fibrillation, complete atrioventricular block, and an inferior wall scar.

In 1966 he was admitted because of progressive exertional dyspnea. In addition to the systolic murmur previously described, a Grade III/VI apical diastolic rumble also was heard. He improved with bed rest, salt restriction, and diuretics.

At the time of his admission in November, 1967, his blood pressure was 110/50 and pulse 40. He appeared chronically ill. There was no jugular venous distension at 45 degree recumbency. The breath sounds were distant and a few râles were heard at the right lung base. The first heart sound was moderately loud. There was a Grade III/VI apical holosystolic murmur and a long Grade III/VI diastolic rumble. An opening snap was not heard. The liver was 16 cm. in height and there was no peripheral edema.

The volume of packed red cells was 42 ml. per 100 ml. and the leukocyte count was 5,850 per mm.³ with 55 polymorphonuclears, 34 lymphocytes, 7 monocytes, 2 eosinophils, and 2 basophils. The urinalysis was normal. Blood urea nitrogen was 32 mg. per 100 ml. and the serum creatinine 2.5 mg. per 100 ml. The serum electrolytes were normal. The electrocardiogram was interpreted to show atrial fibrillation with complete atrioventricular block and an inferior wall scar. The chest roentgenogram was interpreted to show left atrial enlargement, mitral valve calcification, mild pulmonary vascular congestion, and fibronodular disease in both lungs. His dyspnea diminished following a 9 lb. diuresis.

In April, 1968, he was admitted to a hospital in another city with findings of an acute abdominal crisis. He died 3 days after admission.

A postmortem examination was performed. The cause of death was acute infarction of the small intestine secondary to mesenteric artery occlusion.

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right ventricle (i e moderator band or mural trabeculation) Since nerve fibers were not found in the excised specimen the findings in our case resemble more the intimal lesions of peripheral arteries than the heart lesions described by Pung If so it behooves us to look for other vascular lesions in this child and in any others with this syndrome.

Neurofibromas are believed to be benign tumors of the sheath of Schwann Since an extensive plexus of sympathetic and parasympathetic nerve fibers surround the heart and penetrate the epicardium and myocardium the origin of the tumors in Pung s case are easily explained However when the lesion is a fibrous thickening of the endocardium as in our case the etiology is less clear Reubi[8,9] believed that fibrotic lesions were common in von Recklinghausen s disease having found them in small vessels of the kidney endocrine system gastrointestinal tract, and heart but not in such large vessels as the renal artery or aorta Feyrter[10] also described fibrotic lesions in the vascular system but believed they originated as connective tissue possibly of the neural sheaths

That fibrotic lesions which cannot be directly related to neural origin do occur in large vessels in this syndrome is now well established (i e. heart [7] carotid artery [6] aorta [5] renal artery[1-6]) Since the manifestations are acquired rather than congenital we believe that neurofibromatosis resembles idiopathic hypercalcemia and rubella syndromes two other disorders which might more properly be classified as acquired rather than congenital heart disease.

Summary

A case of severe acquired localized right ventricular obstruction in an 8½-year-old child with von Recklinghausen s syndrome is presented The similarity of this case to vascular involvement in previously reported cases is pointed out. It is suggested that vascular lesions in neurofibromatosis may have varied manifestations and that this syndrome should be thought of in the future as a generalized disease which may affect any part of the cardiovascular system For the lesion here reported excision of the fibromuscular band has resulted in disappearance of her pressure difference murmur and right heart failure.

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Case report

This 71-year-old Caucasian married male was admitted to the Salt Lake City Veterans Administration Hospital on Nov. 18, 1967, because of exertional dyspnea and fatigue. The patient was told he had a heart murmur and was given a medical discharge from the military service during World War I following an attack of acute rheumatic fever.

He had no cardiorespiratory symptoms until 1940 when he began having left anterior chest pain usually related to exertion and relieved by rest. In 1960 he noted the onset of progressive exertional dyspnea, easy fatigability, intermittent pedal edema, and orthopnea.

He was admitted to this hospital for the first time in 1963 because of a urinary bladder calculus, at which time he was noted to have a Grade III/VI apical holosystolic murmur. An electrocardiogram was interpreted to show atrial fibrillation, complete atrioventricular block, and an inferior wall scar.

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In April, 1968, he was admitted to a hospital in another city with findings of an acute abdominal crisis. He died 3 days after admission.

A postmortem examination was performed. The cause of death was acute infarction of the small intestine secondary to mesenteric artery occlusion.

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This study was supported by grants from the United States Public Health Service (5 T2 HE 207) and the Utah Heart Association.

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The mesenteric artery occlusion was thought to be due to embolism from a large mural thrombus in the dilated left atrium The mitral valve was fish mouth in appearance and 2 cm long The valve leaflets were fused at the commissures, diffusely thickened and calcified The chordae tendineae were shortened and fused and thickened The other valves appeared normal The left ventricular wall was thickened. There was moderate coronary atherosclerosis. However there was only slight narrowing without any occlusion. There was no evidence of myocardial infarction but microscopically there were scattered areas of fibrosis. The heart weighed 550 grams. Pulmonary congestion was present. There was an old healed infarct in the left kidney

Methods

Hemodynamic studies Right heart catheterization was performed on Nov 3 1966, using a No 7 Lehman catheter introduced via cutdown of a right medial antecubital vein A No 6 Goetz bipolar pacing catheter was introduced through the same vein and advanced to the apex of the right ven

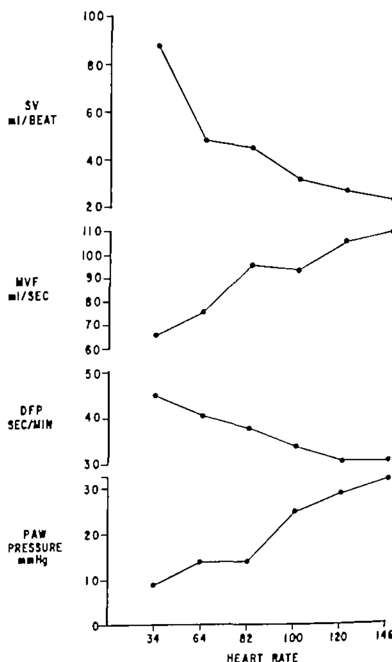


Fig 1 The relationship between stroke volume (*SV*), mitral valve flow (*MVF*), diastolic filling period (*DFP*) and pulmonary artery wedge pressure (*PAW*) during the first study at rates of 34 64 82 100 120 and 146 beats per minute.

tricle. A No. 18 Cournand needle was inserted in the left brachial artery for the measurement of arterial pressure and for the collection of blood samples. Cardiac pacing was performed using a stimulus intensity of 2 milliamperes.

Right heart and arterial pressures measured with Statham P23Db pressure transducers and an electrocardiogram were recorded on an oscillographic recorder (Electronics for Medicine Model DR 12 White Plains, N. Y.). Cardiac output was measured by the direct Fick method.

Pressure and cardiac output measurements were obtained at the patient's inherent ventricular rate, and at artificially paced rates of 64, 82, 100, 121, and 146 per minute. Pacing was carried out for at least 5 minutes at each rate before the hemodynamic measurements were made.

The second study was performed on Nov. 30, 1967. In addition to right heart catheterization, a No. 8 Shirey catheter was introduced via a right brachial arteriotomy and advanced to the left ventricle. This allowed simultaneous measurement of left ventricular and pulmonary artery wedge pressures for the determination of the diastolic pressure gradient across the mitral valve at each pacing rate. Pressure and cardiac output measurements were made at the patient's inherent ventricular rate and at artificially paced rates of 60, 90, and 120 per minute. Mitral valve gradient was obtained by planimetry and the area calculated according to the Gorlin formula.

Results

The results of the first study are listed in Table I. The cardiac output was consistently low with the highest value occurring at a rate of 82 per minute. Despite the higher oxygen consumption at the faster pacing rates, only small increases in cardiac output occurred. A steady decline in stroke volume occurred with increasing heart rate. The pulmonary artery pressure rose steadily with increasing heart rate.

In Fig. 1 the relationship between stroke volume, mitral valve flow, diastolic filling

Table I. Summary of results of the first cardiac catheterization

Parameters	Rate (beats/min.)					
	54	64	82	100	121	146
$\dot{V}_{O_2}$ (ml./min.)	195	194	241	247	272	303
Ca-$\bar{v}_{O_2}$ (vol. %)	6 4	6 3	6 5	7 7	8 2	8 9
CO (L./min.)	3 0	3 1	3 7	3 2	3 3	3 4
CI (L./min./M.²)	1 9	1 9	2 3	2 0	2 1	2 1
SV (ml./beat)	[illegible]	48	45	32	27	23
Pressures (mm. Hg)						
$\overline{PAW}$	9	14	14	25	29	32
PA S/D (mean)	$\frac{36}{10}$ (20)	$\frac{34}{15}$ (21)	$\frac{33}{17}$ (23)	$\frac{42}{25}$ (32)	$\frac{42}{28}$ (33)	$\frac{48}{33}$ (41)
RV S/D	$\frac{34}{4}$	—	—	—	—	—
$\overline{RA}$	3	—	—	—	—	—
BA S/D (mean)	$\frac{143}{52}$ (74)	$\frac{132}{65}$ (88)	$\frac{131}{70}$ (91)	$\frac{144}{81}$ (103)	$\frac{141}{81}$ (103)	$\frac{124}{78}$ (94)
PARI (units)	5 8	3 1	3 9	4 5	1 9	4 3

Abbreviations. $\dot{V}_{O_2}$, Oxygen consumption; Ca-$\bar{v}_{O_2}$, arteriovenous oxygen difference; CO, cardiac output; CI, cardiac index; SV, stroke volume; $\overline{PAW}$, mean pulmonary artery wedge pressure; PA, pulmonary artery; RV, right ventricle; $\overline{RA}$, mean right atrium; BA, brachial artery; PARI, pulmonary arteriolar resistance index (mm. Hg/L./min./M.²).

The mesenteric artery occlusion was thought to be due to embolism from a large mural thrombus in the dilated left atrium. The mitral valve was fish mouth in appearance and 2 cm long. The valve leaflets were fused at the commissures, diffusely thickened and calcified. The chordae tendineae were shortened and fused and thickened. The other valves appeared normal. The left ventricular wall was thickened. There was moderate coronary atherosclerosis. However, there was only slight narrowing without any occlusion. There was no evidence of myocardial infarction but microscopically there were scattered areas of fibrosis. The heart weighed 550 grams. Pulmonary congestion was present. There was an old healed infarct in the left kidney.

Methods

Hemodynamic studies. Right heart catheterization was performed on Nov. 3, 1966, using a No. 7 Lehman catheter introduced via cutdown of a right medial antecubital vein. A No. 6 Goetz bipolar pacing catheter was introduced through the same vein and advanced to the apex of the right ven-

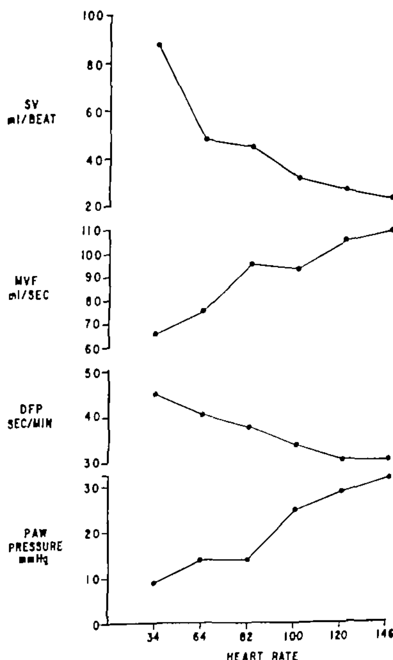


Fig. 1. The relationship between stroke volume (*SV*), mitral valve flow (*MVF*), diastolic filling period (*DFP*) and pulmonary artery wedge pressure (*PAW*) during the first study at rates of 34, 64, 82, 100, 120 and 146 beats per minute.

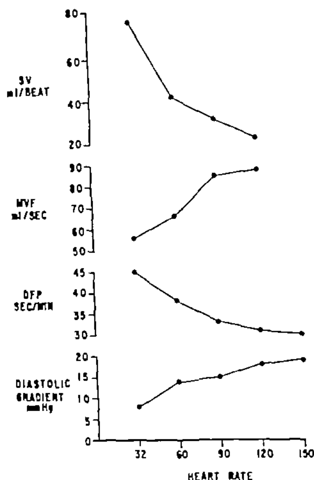


Fig 2 The relationship between stroke volume (*SV*), mitral valve flow (*MVF*), diastolic filling period (*DFP*) and the diastolic gradient across the mitral valve during the second hemodynamic study at rates of 32, 60, 90 120, and 150 beats per minute

Discussion

The patient's symptoms were typical of those associated with mitral valve disease. He had exertional dyspnea for at least 8 years prior to death but there were no episodes suggestive of pulmonary edema. It may be postulated that the patient was protected from pulmonary edema despite the presence of severe mitral stenosis by the bradycardia associated with complete atrioventricular block. The cardiac output which was demonstrated to be low also can be ascribed at least in part to the slow heart rate and represents another factor which mitigated against the occurrence of significant pulmonary venous hypertension and pulmonary edema.

The presence of the apical systolic murmur suggests that the patient had mitral regurgitation. Unfortunately the hypotensive episode that occurred during artificial pacing at a rate of 150 beats per minute during the second study prevented our performing a left ventriculogram to estimate the degree of mitral regurgitation Since the mitral valve area was calculated according to the Gorlin formula without taking into account increased mitral valve flow due to mitral regurgitation, the orifice would be larger if mitral regurgitation were present. As calculated, the valve area was well below the critical size. Unfortunately the description of the valve at the time of the postmortem examination was not de-

Table II Summary of results of the second hemodynamic study

Parameters	Rate				
	32	*60*	*90*	*120*	*150*
V_{O_2} (mL/min.)	184	184	199	206	—
Ca $\bar{v}_{O_2}$ (vol %)	7 5	7 3	7 2	7 5	—
CO (L /min.)	2 5	2 5	2 8	2 7	—
CI (L/min./M ²)	1 5	1 5	1 7	1 6	—
SV (ml /beat)	78	42	31	22	—
Pressures (mm Hg)					
$\overline{PAW}$	13	14	16	20	18
PA S/D (mean)	$\frac{34}{13}$ (19)	$\frac{32}{17}$ (21)	$\frac{43}{18}$ (25)	$\frac{40}{22}$ (28)	—
RV	—	—	—	—	—
$\overline{RA}$	$\bar{5}$	—	—	—	—
BA S/D (mean)	$\frac{157}{55}$ (78)	$\frac{142}{68}$ (95)	$\frac{138}{79}$ (102)	$\frac{130}{80}$ (99)	$\frac{93}{60}$ (68)
LV	$\frac{157}{5}$	$\frac{142}{2}$	$\frac{138}{0}$	$\frac{130}{0}$	$\frac{93}{3}$
PARI (units)	4	4 7	5 3	5 0	—
MVA (cm ²)	0 6	0 6	0 7	0 7	—

Abbreviations as in Table I LV Left ventricular pressure MVA, mitral valve area.

period and pulmonary artery wedge pressure at the different pacing rates is shown Despite the fact that the stroke volume fell with increasing heart rate mitral valve flow increased as the diastolic filling period shortened The pulmonary artery wedge pressure rose as mitral valve flow increased

The results of the second hemodynamic study (Nov 30 1967) are listed in Table II The variation in oxygen consumption at each pacing rate was quite small in contrast to the first study The cardiac output was slightly lower than before and there was no significant change at the different pacing rates. Pulmonary artery wedge pressure increased and left ventricular diastolic pressure decreased with increase in the heart rate leading to an increase in the diastolic gradient across the mitral valve. As the heart rate was increased to 120 beats per minute there was a steady decline in systolic arterial pressure and a rise in diastolic pressure. In Fig 2 it can be seen again that despite a decline in stroke volume with increasing heart rate the mitral valve flow increased as the diastolic filling period decreased Similarly the diastolic pressure gradient increased as the flow increased The effect of increasing the heart rate on the diastolic gradient across the mitral valve is shown in Fig 3

An attempt was made to obtain hemodynamic data at a rate of 150 during the second study Within a few seconds the systemic arterial pressure fell to 93/60 (Fig 3) and the patient complained of dizziness. Because of the hypotensive response the pacing rate was reduced before cardiac output could be measured. During this short period of pacing the mitral diastolic gradient fell very slightly in comparison to that measured at a pacing rate of 120 This is in marked contrast to the response in 1966 in which the arterial pressure fell very slightly but the pulmonary artery wedge pressure rose.

There was excellent agreement among the mitral valve areas calculated at the different pacing rates.

pulmonary edema. The fall in cardiac output however was detrimental to the cerebral circulation in that the patient developed dizziness. Thus the response on one occasion to a rapid ventricular rate was further rise of pulmonary artery wedge pressure with no fall in cardiac output whereas at another time the cardiac output presumably fell accompanied by a fall in arterial and pulmonary artery wedge pressure. Which of these responses to a rapid ventricular rate will occur in a patient with mitral stenosis and the factors governing them is not known.

The increase in the mitral diastolic gradient at the higher pacing rates was due primarily to a rise in pulmonary artery wedge pressure but left ventricular diastolic pressure also fell. This can be explained on the basis of smaller end-diastolic residual and stroke volumes associated with diminished ventricular filling consequent upon a shortened diastolic filling period.

Summary

A patient with mitral stenosis with atrial fibrillation and complete heart block has been presented. Hemodynamic studies were performed to examine the effect on the mitral diastolic pressure gradient of changes in the diastolic filling period induced by artificial ventricular pacing over a rate range of 32 to 150 per minute. An increase in the heart rate was accompanied by a decrease in the diastolic filling period, increase in the mitral valve flow, and an increase in the pressure gradient across the mitral valve. Low cardiac output associated with a long diastolic filling period probably explains the absence of a history of pulmonary edema despite the presence of significant mitral stenosis. During the first study the pulmonary artery wedge pressure rose slightly and the systemic arterial pressure fell slightly during pacing at a rate of 146 per minute whereas during the second study hypotension (presumably secondary to a fall in cardiac output) and a slight fall in pulmonary artery wedge pressure occurred during pacing at 150 per minute. The type of response to a rapid ventricular rate that will occur in a patient with mitral stenosis and the factors governing these responses are not known.

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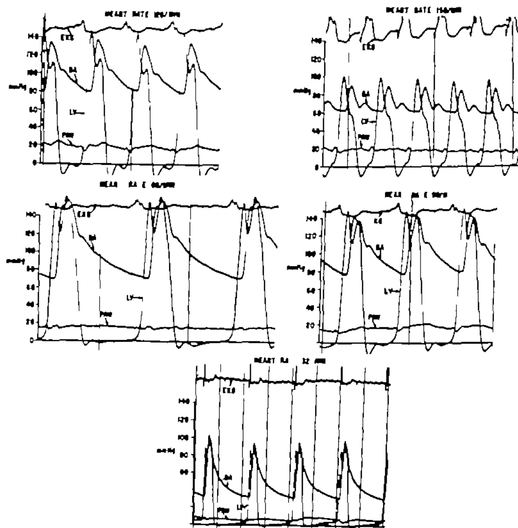


Fig 3 Simultaneou recording of the electrocard ogran (*EKG*) brachial artery pres ure (*B A*) left ventricular pres ure (*LV*) and pulmonary artery wedge pressure (*P W*) at heart rates of 32 60 90 120 and 150 beats per minute All pressures are recorded using the same zero base line and transducers of equal sensit v ty The pres ure calibration show to the left of each recording All record ngs were made at a paper speed of 100 mm per second Th vertical lines are one second time lines

tailed enough to provide a check on the calculated area.

The influence of the diastolic filling period on the diastolic gradient across the stenotic mitral orifice is well demonstrated by the hemodynamic data Although the patient s cardiac output was relatively constant the mitral valve flow increased as the diastolic filling period shortened with an increase in heart rate These changes were accompanied by a rise in pulmonary artery wedge pressure and an increase in the pressure gradient across the mitral valve It is this mechanism that leads to the occurrence of dyspnea and even pulmonary edema in patients with mitral stenosis when the heart rate in creases due to a change from sinus rhythm to atrial fibrill ition with a rapid ventricular response

It is of interest that during the first study during pacing at a rate of 146 beats per minute the pulmonary artery wedge pressure rose and was accompanied by a small decline in systolic arterial pressure. How ever during the second study at a pacing rate of 150 beats per minute the systemic arterial pressure fell significantly and was accompanied by a slight decline in pul monary artery wedge pressure The abrupt fall in arterial pressure during the second study presumably was due to a fall in cardiac output. Such a fall in output de spite the fast rate prevents a rise in pul monary artery wedge pressure and thus protects the lungs from the occurrence of

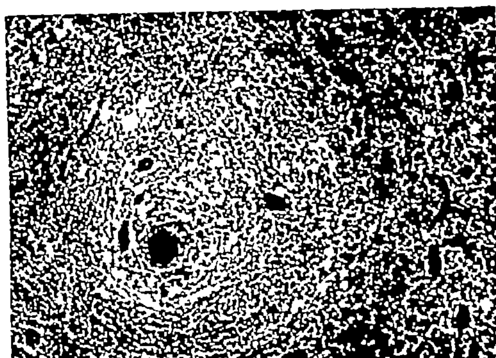


Fig. 3 Germinal center in the spleen with giant cells and round cell infiltration

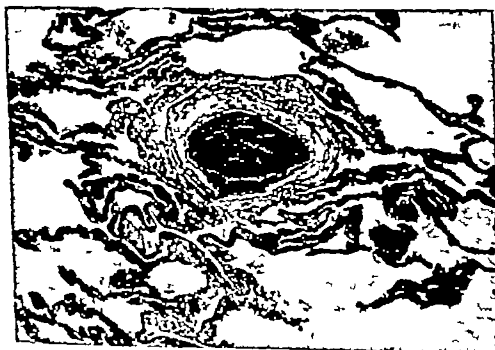


Fig. 4 Moderate thickening and fraying of the pulmonary artery Slight perivascular inflammation.



Fig. 1. Inflammation in and surrounding the renal artery.

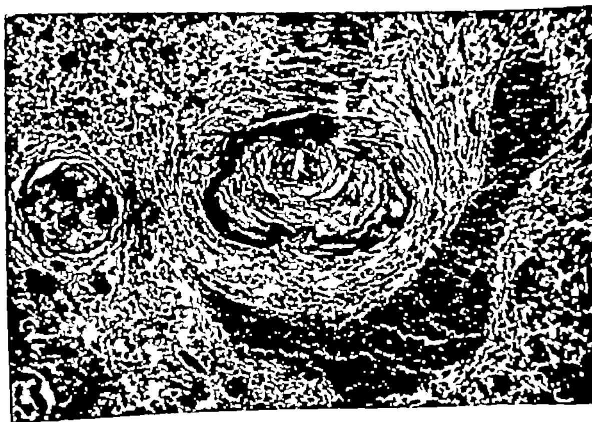


Fig. 2. Large renal artery with marked intimal proliferation, fraying, and obstruction. Medial and perivascular inflammation.

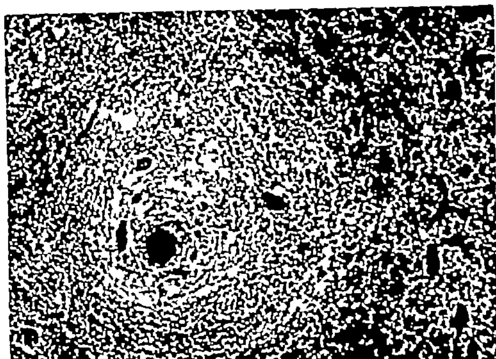


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Fig. 4 Moderate thickening and fraying of the pulmonary artery. Slight perivascular inflammation.

the kidney liver and spleen and the so-called classic or Kussmaul Maier Type [13] involving larger muscular arteries seems clinically and pathologically useful The extensive thoughtful review of Rose and Spencer[14] dividing polyarteritis into two major types those with and without pulmonary involvement seems to at least substantiate the idea of clinicopathologic divisions. They could however find little evidence for a drug etiology but instead implied a relationship to beta hemolytic streptococcus infection Fordham and associates[15] three cases of polyarteritis nodosa presenting as poststreptococcal glomerulonephritis validate this view at least as one factor in polyarteritis. We feel that the work of Knowles and Zeek[16] best fit the facts in which they describe a classic or Kussmaul's type of lesion involving the medium-sized muscular arterioles of muscle and kidney of different ages but generally not the liver spleen or glomerulus and the hypersensitivity angiitis involving small arterioles and capillaries especially of the lung spleen and kidney usually of the same age It is the latter that seemed to be related to hypersensitivity reaction to drugs.[7, 10] We feel that our patient's clinical and pathologic picture best fit this type

Certainly there is overlap between these two types of lesions described by Zeek[16] as manifested by lesions involving the larger arterioles of the kidney and the lesions of the smaller vessels especially the spleen Nevertheless we feel that this is at least a plausible explanation of the events that occurred We postulate that the patient developed an untoward reaction to allopurinol or one of its metabolites and a florid vasculitis involving the blood vessels of the liver pancreas kidney myocardium and perhaps the brain causing ischemia and necrosis further compromising the circulation in this elderly man in many organs and causing the clinical picture that developed

Etiologic considerations Considerable controversy and confusion exists regarding the pathogenesis of the vasculitides. Although Kussmaul and Maier[13] originally described periarteritis nodosa in 1866 it was not until the first third of this century that fairly clear concepts of etiology were formulated Gruber[17] in Germany in 1925 was probably one of the first to suggest that periarteritis or polyarteritis may be a hypersensitivity phenomenon Clark and Kaplan[18] in 1937 described vascular lesions in serum sickness which seemed to substantiate this idea of hypersensitivity Considerable impetus was given to this concept by the work of Rich and associates[19] at the Johns Hopkins Hospital when they described polyarteritis in serum sickness cases on sulfonamide treatment in 1942 and by their experimental study in 1943[20] in which they described experimental evidence for hypersensitivity and polyarteritis. Hawn and Janeway[21] in 1947 working with bovine gamma globulin seemed to extend and confirm this concept.

In more recent work at the Johns Hopkins Hospital (1958) Germuth and coworkers[22, 23] described lesions in rabbits similar to active serum sickness due to antigen-antibody combination

Dixon and co-workers[24] in 1960 related the abnormality of hypersensitivity vasculitis to soluble antigen antibody complexes damaging small blood vessels. Although antibodies to allopurinol or some metabolite of allopurinol in the form of antigen-antibody complexes is by no means proven in this case it is a plausible explanation for the events that occurred

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Hypersensitive vascular reactions have been described with a large number of drugs. A case of the hypersensitivity type of vasculitis with fibrinoid necrosis and eosinophilic reaction involving multiple organs especially the kidney marked by generalized maculopapular body rash resulting in uremia and death has been reported The only possible drug to be implicated was allopurinol (4-hydroxypyrazolo-[3 4-*d*]pyrimidine) a xanthine oxidase inhibitor currently used in the treatment of disorders of uric acid metabolism

The literature concerning hypersensitivity angiitis and the periarteritis polyarteritis entities have been reviewed No previous instances of this type of hypersensitivity angiitis connected with the administration of allopurinol have been reported

It is our feeling that the reported case

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Review

Hemodynamic and vascular responses to antihypertensive treatment with adrenergic blocking agents: A review

Rune Sannerstedt M D
James Conway M D
Ann Arbor Mich

Patients with established uncomplicated arterial hypertension are characterized by a normal resting cardiac output and an increased systemic vascular resistance affecting the renal vascular bed most prominently [1-3] The elevated blood pressure can generally speaking be lowered by reducing the cardiac output lowering the systemic vascular resistance or through a combination of both An ideal antihypertensive agent should lower the blood pressure by reducing both the systemic and particularly the renal vascular resistance both at rest and during stress situations of various kinds

As this field is reviewed it becomes apparent that the available information on antihypertensive drugs is based mainly on acute animal experiments and parenteral administration to human subjects Our knowledge on possible changes induced by long term treatment is poor This discussion therefore considers three widely used hypotensive agents with adrenergic blocking properties—Rauwolfia preparations guanethidine and methyldopa—and separately deals with (1) acute effects, (2) effects of short term treatment (less than 4 weeks) and (3) effects of long term treatment

Rauwolfia preparations

Acute effects Only two studies of the acute effects on cardiac hemodynamics are available [4,5] In one of them the effect of 2 5 mg of reserpine given intramuscularly was observed 4 hours after administration[4] The blood pressure dropped in all cases In patients with borderline hypertension and elevated cardiac output the cardiac output decreased while in those with normal cardiac output but elevated systemic vascular resistance the latter decreased The heart rate did not change During head up tilting five of eleven reserpine-treated patients fainted indicating an orthostatic action which is not generally seen with this agent In the other study on only four subjects, both cardiac output and systemic resistance fell after intravenous administration of 1 0 to 5 0 mg [5]

After intravenous administration of reserpine a slight reduction in glomerular filtration rate was noted and the excretion of water and electrolytes decreased

Parenteral reserpine increased digital blood flow significantly in both normotensive and hypertensive subjects.[7] The mean blood pressure and systemic resistance fell without consistent changes in heart rate

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The overshoot of blood pressure following the Valsalva maneuver is not apparently inhibited by reserpine given parenterally in moderate doses but the pressor response to infused norepinephrine may be slightly increased

Effect of short-term treatment Syrosingopine in a dosage of 1 5 to 6 0 mg given intramuscularly daily for seven days to normal volunteers resulted in a lower blood pressure but there were no definite changes in heart rate or cardiac output It did not interfere with the response to recumbent exercise.

In hypertensive patients studied for one week before and after oral syrosingopine it was noted that although the resting arterial pressure was almost brought to normal there was still a considerable pressure rise during sitting exercise Similarly the pressor responses to noxious stimuli such as the cold pressor test were unaltered [11]

In hypertensive patients oral reserpine in large doses resulted in a marked reduction in systemic resistance and even an increased cardiac output after one week of treatment while renal blood flow decreased and renal resistance increased [12]

Effects of long-term treatment In the study mentioned above the systemic resistance continued to be reduced after 6 weeks of treatment but the renal blood flow had returned to about control levels.[12] Likewise the renal hemodynamics in hypertensive patient treated for three months with oral reserpine 3 0 to 6 0 mg daily did not show consistent changes

After three months of treatment with oral reserpine dosage of 0 75 mg daily a fall in both resting and exercising blood pressure levels was reported to occur in hypertensive patients [14] The decrease was felt to be due to lowered resistance as there were no changes in the resting cardiac output or the output response to exercise

Reserpine was shown to block both arterial and venous reflex vasoconstriction in normal subjects after oral treatment for up to four months

The weight gain seen during treatment with Rauwolfia drugs is probably not due to fluid retention in most of the cases as the extracellular fluid volume was shown to maintain a constant ratio to total body weight after reserpine given orally from four weeks to four months.[12] This is supported by studies on the body fluid compartments before and after parenteral administration of reserpine for six days [1]

Conclusion Most authors report a favorable pattern of response to oral reserpine with lowered systemic vascular resistance as the main feature without reduction in the renal blood flow There is conflicting evidence concerning the effect of reserpine on the hemodynamic responses to stressful procedures.

The weight gain seen during treatment with Rauwolfia preparations is probably not due to fluid retention It should also be noted that most of the data for reserpine were obtained for dosage levels which are not recommended for continued therapy

Guanethidine

Acute effects The acute effects of parenterally administered guanethidine usually in doses of 10 to 25 mg intravenously have been studied by several authors. [22] Within 10 minutes after an intravenous injection there is usually a short lived pressor phase with increased systolic and diastolic pressures in both normotensive and hypertensive subjects.[20] The depressor phase which follows is characterized by a substantial reduction in cardiac output. The systemic resistance is not altered.[22] The effect on the heart rate is variable [16] In patients with pulmonary hypertension there is a reduction in pulmonary pressure without change in pulmonary resistance In normal subjects and in patients with arterial hypertension a small reduction in pulmonary vascular resistance has been described [1]

After taking guanethidine intravenously the response to supine exercise has been reported to be largely unchanged in both normotensive and hypertensive subjects, but the increase in heart rate was smaller The blood pressure increased in the same manner as in the control study

The reduction in cardiac output at rest in recumbency is accompanied by a decrease in renal blood flow and glomerular filtration rate In both normotensive and hypertensive subjects the water and sodium excretion diminish [22,24] The cerebral and hepatoportal blood flows have been reported to fall [26] If the patient is tilted a further decrease of both the blood pressure

and cardiac output is obtained and systemic resistance falls [22]

The blood pressure overshoot following the Valsalva maneuver is completely blocked by guanethidine and other vasoconstrictor reflexes are markedly inhibited [19,20,22] The response to tyramine and *ephedrine infusions is not significantly* altered but the pressor effect of single doses of norepinephrine is enhanced [20,23]

Effects of short-term treatment After 4 to 10 days of oral guanethidine the cardiac output *in hypertensive patients was lower* in the recumbent position and the decrease became more marked after tilting while the systemic resistance was only moderately lowered [26] The heart rate decreased and an impaired pressor response to noxious stimuli such as the cold pressor test was reported [27]

Both the *renal* plasma flow and glomerular filtration rate were found to decrease in hypertensive subjects but the vascular resistance was unchanged [26] These changes became more marked after tilting In nor*mal subjects, on the other hand an in*creased renal blood flow and a decreased resistance after taking oral guanethidine in a dosage of 10 mg daily for 5 to 7 days have been described [24]

The digital vascular reactivity to norepinephrine increased after oral guanethidine given to hypertensive patients but the *drug did not produce vasodilatation in* the digit with the subjects in the resting recumbent position [28] In normal subjects the drug was shown to block both arterial and venous vasoconstriction [14]

Effects of long-term treatment After stabilization of the blood pressure on treatment of 12 patients with oral guanethidine neither supine *nor standing cardiac output* was significantly changed and the systemic vascular resistance was lower [22,23] The heart rate had decreased On walking the systemic pressures of the hypertensive subjects were *lower* than before treatment with no significant change in cardiac output.[29] Others observed *a fall in* blood pressure instead of the usual increase during exercise with guanethidine [30]

Guanethidine in large oral doses to normal subjects for four weeks resulted in a lower resting heart rate, but there were no significant *changes* in mean arterial pressure or cardiac index.[22] During supine exercise the cardiac index and mean pressure were lower than in the control study

After 8 to 30 days of oral guanethidine, in patients with severe hypertension the renal plasma flow and glomerular filtration rate were found to be decreased in both the lying and standing positions, as were the excretion of sodium potassium and water [2]

The blood volume has been reported to be significantly increased in hypertensive patients after oral guanethidine for 7 to 21 days.[32] *Similar results were found after one* year of treatment.[34] Total exchangeable sodium increased and creatinine clearance fell In normal subjects, on the other hand, oral guanethidine for 7 to 21 days was found to *increase* the plasma volume without any sodium retention.[35]

Conclusion There are a fairly large number of reports on the acute and subacute effects in man of guanethidine, but long-term studies are few

The hemodynamic responses to guanethidine are similar to those with ganglionic *blocking agents. The main immediate* effect is probably on the cardiac output, leaving the systemic vascular resistance little changed but the long term studies indicate that cardiac output may return to normal Hypotension during exercise can occur

Impairment of the renal blood flow is to *be anticipated during treatment* with guanethidine The weight gain seen is due to increased plasma volume, probably secondary to sodium retention

Methyldopa

Acute effects The decrease in recumbent blood pressure, seen after parenteral admin*istration of methyldopa to hypertensive* patients, is ascribed by some authors to a lower systemic vascular resistance with only minor changes in the cardiac output.[23,36] Renal vascular resistance is reduced substantially and therefore the renal blood flow and glomerular filtration rate are left uncompromised despite the blood pressure reduction

It has been reported that the same pattern of systemic and renal hemodynamic *changes is maintained while in the* erect position and the increase in systemic and renal resistance seen after tilting in the

control state is abolished after methyl dopa.[39]

Different results have, however been reported by others, who have found the blood pressure reduction to be due to a decreased output with an unchanged systemic vascular resistance.[37,4] The heart rate fell significantly in one study [37] but not in another where it even increased when methyldopa was given to a series of labile hypertensives.[38] Also in that series, the recumbent blood pressure reduction was due to a decreased cardiac output However the greater reduction in mean blood pressure with 60 degree head-up tilting occurred without a further reduction in cardiac output, and the systemic resistance was lowered in this position. This was thought to be due to orthostatic loss of reflex arteriolar constriction.

Methyldopa given intravenously has not been shown to produce consistent effects on the hypertensive overshoot seen after the Valsalva maneuver [37]

Effects of short-term treatment After taking oral methyldopa for 7 to 16 days, the blood pressure in hypertensive patients fell without change in cardiac output, indicating a lowered systemic resistance. The heart rate was unchanged. Tilting feet downward did not produce an exaggerated fall in blood pressure or cardiac output when compared with the control study [40]

During upright exercise, the blood pressure level was reported to be markedly lower than before treatment but without tendency to exercise hypotension.[31,42,43] The pressor response to noxious stimuli, such as the cold pressor test, was described to be impaired in hypertensive patients on oral methyldopa,[37] and the response to the Valsalva maneuver was completely abolished in eight of ten patients after oral treatment with methyldopa.[39]

Oral methyldopa taken for 6 to 19 days on the whole did not produce consistent changes in glomerular filtration rate.[39] Patients responding to methyldopa with a blood pressure decrease showed an increased renal blood flow with lower calculated renal vascular resistance. These results have been confirmed for hypertensive patients with reduced renal function.[41]

The pressor response to norepinephrine was only slightly increased but strikingly prolonged after treatment with methyl dopa.[44] After tyramine, on the other hand the pressor effect was markedly enhanced An increased digital vascular reactivity to norepinephrine has also been demonstrated.[35] The drug produces significant digital vasodilatation in the recumbent hypertensive patient [35] and blocks both arterial and venous reflex vasoconstriction in normal subjects.[31]

When administered as therapy for hypertensive patients, methyldopa has been shown to have a smaller orthostatic effect than guanethidine for a given change in recumbent blood pressure [31,44]

Effects of long-term treatment After stabilization of therapy on oral methyldopa the systemic resistance was lower in both the supine and standing positions in eight of ten hypertensive patients studied.[39] The heart rate was also reduced On walking the blood pressure level was lower than before treatment. The exercise cardiac output was nevertheless, more than 20 per cent higher than in the control study resulting in markedly lower resistance levels during exercise

Conclusion Though opinions differ it seems that methyldopa acts primarily to reduce systemic resistance with no appreciable effect on cardiac output.

Hypotension during exercise does not occur The renal blood flow appears to be maintained. However little information is available on the long-term effect.

Summary

While the pharmacological effects of the three agents discussed (reserpine derivatives, guanethidine and methyldopa) appear to depend upon interference with sympathetic nervous activity they differ in their effects in man.

After acute administration, there is a fall in blood pressure with each agent, but with reserpine and methyldopa, cardiac output is little affected With methyldopa the renal resistance appears to fall. Guanethidine produces a sharp fall in the cardiac output and renal blood flow

After treatment for a few days with these agents, the differences in their actions are less apparent and from the very limited information available on long-term

therapy each of these agents achieves its hypotensive effect without reduction in cardiac output The renal blood flow remains at control levels with reserpine and methyldopa but is still somewhat reduced with guanethidine

From the practical point of view therefore the decision to use one or another of these agents should rest upon differences in their clinical effectiveness and side effects There is an urgent need for information on the changes in the action of these drugs during long term therapy These changes could be caused by the drugs pharmacological effects or by physiological adaptations within the patient

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Propranolol as an antihypertensive agent

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Potent drugs usually used at present in the treatment of hypertension act to interfere with the sympathetic supply to blood vessels. These drugs have differences in the degree to which they modify cardiovascular responses [9,11,17] but they all have an enhanced hypotensive effect under physiological conditions that require increased vasoconstrictor activity to maintain the blood pressure There is therefore an increased fall of blood pressure due to interference with the venous return as seen from the effect of gravity on assuming the erect posture or from obstruction of venous return as in defecation or Valsalva's maneuver Increased demand of various vascular beds *muscle on exercise skin in a* hot environment, and probably splanchnic after a meal all tend to lower the blood pressure in the presence of inhibition of the sympathetic to blood vessels. The diurnal variation with a reduced blood volume at the earlier part of the day also necessitates sympathetic activity to maintain blood pressure. The effect of these physiological stresses is additive There is, therefore, a need for a potent agent that will lower the blood pressure without interfering with cardiovascular control of blood vessels. The beta adrenergic blocking drug propranolol may meet this criterion

Patients

The earlier work with propranolol (and pronethalol) in hypertension has been previously summarized [9] Subsequently Prichard and Gillam[14] have reported a series of 109 patients treated for up to 4 years. The drug was withdrawn in 4 at an early stage before response could be assessed (for reason see side effects) Of the remaining (105) patients 78 had essential hypertension and the rest had renal hypertension There were electrocardiographic (ECG) changes of left ventricular hypertrophy in 71 patients blood urea was over 40 mg per 100 ml in 57 initially fundi were Grade IV in 18 III in 9 II in 48, I in 27 normal in 3 In 5 of these 105 patients the drug was subsequently withdrawn

Blood pressure control

There were a large number of patients in the series who had previously been treated with sympathetic inhibitory drugs. This enables some comparison of the merits of propranolol and these drugs. Therapy was changed to propranolol because of adverse side effects on the previous drug or poor control particularly of the supine pressure There were 28 patients previously on bethanidine 16 of whom had supine or standing diastolic pressures of 100 mm. Hg or less on this drug while 23 patients reached this level on propranolol Only 4 patients had supine *and* standing diastolic pressures of 100 mm Hg or less on bethanidine whereas there were 17 on propranolol The average level of blood pressures

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for these 28 patients on bethanidine were 197/114 mm. Hg supine, 152/102 mm. Hg standing, and 126/81 mm. Hg after exercise (ascending and descending 18 stairs), while on propranolol the blood pressure was 162/94 mm. Hg supine, 151/100 mm. Hg standing, and 163/100 mm. Hg after exercise. In a group of 11 patients treated with guanethidine, 6 patients had supine or standing diastolic pressures of 100 mm. Hg or less and in 3 patients both pressures were at this level; after treatment with propranolol there were 11 and 8 patients with these pressures, respectively. The average blood pressures on guanethidine were 19 /109 mm. Hg supine, 161/98 mm. Hg standing, and 128/72 mm. Hg after exercise; on propranolol they were 156/95 mm. Hg supine, 145/94 mm. Hg standing, and 133/8 mm. Hg after exercise. Methyldopa was the previous drug in a group of 30 patients and on this drug 18 patients had supine or standing pressures of 100 mm. Hg or less, 11 patients had this pressure in both positions. When propranolol was given to these patients there were 29 and 22 patients with these pressures, respectively. On methyldopa the average supine blood pressure was 162/102 mm. Hg; it was 142/88 mm. Hg on propranolol. In the standing position the blood pressures 152/104 mm. Hg on methyldopa and 136/93 mm. Hg after treatment with propranolol, while after exercise the figures were 154/98 and 143/92 mm. Hg, respectively. In all these groups of patients, approximately equal numbers had diuretics while on the previous drug and while on propranolol. The remaining patients consisted of 11 who had propranolol added to bethanidine, guanethidine, or methyldopa, 10 on thiazides or reserpine, 15 previously untreated; in all of them propranolol improved control.

In the whole series, 9 (84 per cent) of the original 109 achieved a diastolic blood pressure of 100 mm. Hg or less, which compares favorably with series of patients treated with other drugs, although comparison between different series of patients from different centers is difficult.

Response to posture and exercise

The absence of postural and exercise hypotension on propranolol is a feature of

Table I

Drug	Average blood pressure (mm. Hg)		
	Supine	Standing	Exercise
Bethanidine (N = 17)	180/114	134/94	127/82
Guanethidine (N = 16)	176/108	141/92	132/81
Methyldopa (N = 15)	154/103	127/94	131/89
Propranolol (N = 17)	143/90	135/94	140/92

blood pressure control with this drug; supine pressure is satisfactorily controlled. This point was further illustrated by examining in more detail blood pressures of 17 patients who had previously taken part in a within-patient comparison of bethanidine, guanethidine, and methyldopa and who were subsequently given propranolol. In all cases patients had been under prolonged observation and for each patient the average of the blood pressures measured on 7 separate consecutive visits to these outpatients is given in Table I.

Hemodynamic studies in 9 patients treated for at least 7 months from this series have confirmed that blood pressure does not fall either on standing or on severe exercise.[10] There is also no postural or exercise hypotension after intravenous propranolol,[11] but here only minimal hypotensive effect is seen.

Other evidence of unimpaired vasomotor control

Propranolol does not inhibit the vasoconstriction that occurs during Valsalva's maneuver either after intravenous administration[12] or after prolonged oral administration.[13, 14] Valsalva's maneuver is modified as intravenous propranolol reduces pressor overshoot, no doubt due to a reduction in the cardiac contribution to this overshoot; a similar effect was seen from pronethalol.[14]

Raising environmental temperature (from 7 to 30° C.) increases the postural drop of blood pressure in hypertensive patients treated with bethanidine or guanethidine; this is due to increased dilatation of skin

vessels with the absence of adequate compensatory constriction in other vascular beds High environmental temperature does not result in a postural fall of blood pressure in patients being treated with propranolol [14,15]

Effect of propranolol on cardiac output

Intravenous propranolol reduces cardiac output when supine [24] standing and after exercise [21] Prolonged oral propranolol also reduces cardiac output when supine [8] standing and after exercise[18] with the fall in cardiac output there is a rise in peripheral resistance

Propranolol and other hypotensive drugs

As mentioned above in the present series approximately equal numbers of patients received diuretics on propranolol and on bethanidine guanethidine or methyldopa and in 11 propranolol was given in combination with bethanidine guanethidine or methyldopa [14] These latter drugs may be given in gradually reduced doses during the transitional period of change to propranolol and are only rarely needed on a more prolonged basis

Side effects

There are two untoward effects from propranolol that are potentially dangerous but they can be avoided with foresight in patient selection The drug should not be given to patients with obstructive airways disease as endogenously maintained bronchial dilatation may be antagonized and airways resistance increased Patients in heart failure or patients with a history suggestive of left ventricular insufficiency (even without signs of heart failure on physical examination or chest roentgenogram) are critically dependent on sympathetic activity to the heart to maintain their cardiac output. These patients should not be given propranolol without prior administration of digitalis and diuretics. If these measures alleviate the dyspnea it is reasonable to start the patient on propranolol Uncontrolled heart failure is a contraindication to propranolol

It should be emphasized that the risk of precipitating heart failure is relatively greater at the onset of treatment. The small percentage increase in dose at high dose levels entails less risk of suddenly precipitating heart failure than when the dosage is commenced In our experience, of a total of about 200 patients with dosages up to 1 000 mg q d.s. (as much as needed daily) our only case of sudden cardiac decompensation was at the commencing dose of 10 mg q d.s.

Side effects that patients mentioned spontaneously included[14] cold extremities noticed in cold weather due to reduced peripheral blood flow from propranolol in three [4] tiredness in four and dreams in four which were abolished in three by taking the last dose by 6 30 P.M Slight indigestion abolished by taking the tablets with food occurred in several patients.

Of the original 109 patients, the drug was withdrawn before any blood pressure response could be assessed in 4 patients (all women) It was withdrawn in one because of depression reversed immediately on stopping the drug in one because some shortness of breath on exertion in one because of nausea and heart burn and in a fourth patient because she felt weak and tired

Therapy was withdrawn in 5 further patients because of chronic heart failure associated with chronic renal failure in 2 patients (bethanidine group) a case of indigestion in another patient, failure of control (methyldopa group) and one patient who experienced persistant tiredness (no previous treatment group)

From response to retrospective questioning (in 31 patients) it appears that patients prefer propranolol to bethanidine guanethidine or methyldopa although it should be remembered that patients tend to prefer the most recently administered drug [17] Stephen[illegible] has reviewed the side effects that occur from propranolol

Dosage and other studies

The dosage of propranolol required to lower the blood pressure varies considerably Dosage was commenced at 5 or 10 mg four times daily and increments of about 25 per cent per dose were made at each visit to outpatients, usually every two weeks. If the patient is more closely observed increments may be made more

frequently even daily Dosage was increased until diastolic blood pressures supine and standing were in the range 80 to 100 mm Hg unless the pulse rate fell below 55 beats per minute after resting for 3 minutes on the couch In the present study the largest dosage used was 1 000 mg q.d.s in one patient dosage of over 250 mg q d.s. was not exceptional Some patients needed only *10* to *20* mg q.d.s. Diuretics were used as indicated and in a few instances small doses of other hypotensive drugs were used In severe and moderately severe hypertensive patients, the average dosage was about 100 to 120 mg q.d.s. with about half of the patients needing a diuretic in addition

There appears to be a wide margin of safety with propranolol In a double-blind multidose-level trial of propranolol in angina pectoris, a group of 6 mildly hypertensive patients blood pressure fell from a mean 115 (154/96) standing to a mean of 10? (135/85) ($p < 0.005$) standing as dosage was increased from zero to an average of 320 mg daily doubling the dose resulted in no change of blood pressure—at an average dose of 640 mg daily the standing blood pressure averaged 103 mm Hg (137 86)

The degree of success that other investigators have found with propranolol is clearly correlated with the dosage used several have used too low a dose or inappropriately have used the same dose for each patient and as would be expected have found little or no effect.[4-7, 19, 20, 21]

Frohlich and associates, in a group of 19 mildly and moderately hypertensive patients, used up to 400 mg a day (average 180 mg) and found propranolol an effective hypotensive drug as have Baczko Dabrowska, and Wocial in 17 patients using up to 320 mg a day and Tewari and Grant[22] in 11 patients taking propranolol alone (up to 400 mg a day) and 13 taking in combination with methyldopa (up to 300 mg a day) Even with these three groups the maximum dose was rather less than the *average* dose that we have found necessary for optimum effect and it seems likely that where indicated greater reduction of blood pressure would have been obtained with larger doses. The only other report of any large series of patients has only been brief but Zacharias[23] has used propranolol for nearly 5 years involving 240 patients and has had a smaller percentage of failures than with any drug used in the last 15 years. Zacharias considers that the dosage that has been used by several investigators has been inadequate.

Onset of action

At an early stage with the use of propranolol it appeared that the full hypotensive effect of a constant dose of propranolol often took some time to reach its maximum formal experiments have confirmed this and examples have been reported [11, 24] The greater part of the hypotensive effect is seen within *2 weeks, but* analysis of a group of patients under constant clinic conditions showed a significant fall of blood pressure between 3 weeks (average supine blood pressure 147/95 after stabilization on propranolol) and one month later (average supine blood pressure 138/87 $p < 0.05$ systolic, $p < 0.005$ diastolic) There was no further drop after a further 2 months the average pulse was the same throughout and dosage was slightly reduced.[24] Analysis of groups of patients on bethanidine guanethidine or methyldopa did not show any delayed fall This further fall after final adjustment of the dose does not present any problem in management as once normotensive levels are reached it usually seems to require a considerable increment of dosage for any further fall in pressure (see above)

In mildly hypertensive patients this delayed fall is not seen the effect is complete within 24 hours.

Other beta receptor blocking drugs

Pronethelol a drug possessing local anesthetic actions like propranolol but in contrast also having some weak sympathomimetic effect, was the first beta receptor blocking drug used to control the blood pressure. This drug has now been withdrawn

N isopropyl-p-nitro phenyl anolamine INPEA, a beta blocking drug without local anesthetic effect also in our experience lowers the blood pressure, although it frequently produced side effects.[11]

Practolol (ICI 50172 Eraldin) which

also has no local anesthetic effect inhibits the sympathetic to the heart but has relatively little effect on the beta actions on peripheral smooth muscle[8] We have been using it in the treatment of hypertension in a series of over 30 patients and find that it too is an effective hypotensive agent.[12]

Mode of action

While it is possible that propranolol exerts its hypotensive effect by some property other than beta receptor blockade it is unlikely The hypotensive effect of other beta receptor blocking drugs supports this view Propranolol lowers cardiac output and as arterial pressure is a function of cardiac output and peripheral resistance lowering cardiac output will tend to lower pressure However after intravenous propranolol there is little effect on arterial pressure[21 24] and the reduction in cardiac output is associated with a rise in peripheral resistance Inhibition of the cardiac sympathetic reduces the cardiac contribution to rises in pressure which are therefore attenuated and there is for instance a reduced overshoot of Valsalva s maneuver[13] a reduced rise in blood pressure on exercise[21] As there is evidence of a delayed onset of full hypotensive effect it has been suggested[13 14] that the reduced pressor responses condition the baroreceptors to produce their inhibitory impulses at a lower level of blood pressure and mean blood pressure falls A similar situation is seen in the hypertensive patient on bed rest this results in a reduction in sensory stimuli hence pressor events and baroreceptors over a period for a few days lower blood pressure by a variable amount

Conclusion

Propranolol is an effective hypotensive drug with a different mode of action from potent drugs in general use It usually gives good control of the supine pressure with no postural or exercise hypotension

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also has no local anesthetic effect inhibits the sympathetic to the heart but has relatively little effect on the beta actions on peripheral smooth muscle[2] We have been using it in the treatment of hypertension in a series of over 30 patients and find that it too is an effective hypotensive agent.[15]

Mode of action

While it is possible that propranolol exerts its hypotensive effect by some property other than beta receptor blockade it is unlikely The hypotensive effect of other beta receptor blocking drugs supports this view Propranolol lowers cardiac output and as arterial pressure is a function of cardiac output and peripheral resistance lowering cardiac output will tend to lower pressure However after intravenous propranolol there is little effect on arterial pressure[21 24] and the reduction in cardiac output is associated with a rise in peripheral resistance Inhibition of the cardiac sympathetic reduces the cardiac contribution to rises in pressure which are therefore attenuated and there is for instance a reduced overshoot of Valsalva s maneuver[13] a reduced rise in blood pressure on exercise[21] As there is evidence of a delayed onset of full hypotensive effect it has been suggested[13 14] that the reduced pressor responses condition the baroreceptors to produce their inhibitory impulses at a lower level of blood pressure and mean blood pressure falls. A similar situation is seen in the hypertensive patient on bed rest this results in a reduction in sensory stimuli hence pressor events and baroreceptors over a period for a few days lower blood pressure by a variable amount

Conclusion

Propranolol is an effective hypotensive drug with a different mode of action from potent drugs in general use It usually gives good control of the supine pressure with no postural or exercise hypotension

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reducing the elevated heart rate, mean systolic ejection rate, and cardiac output that may be associated with thyrotoxicosis. When indicated as an emergency interim measure, propranolol can promptly improve the hyperdynamic cardiovascular manifestations of this metabolic abnormality while awaiting the effects of specific treatment. In the presence of regular sinus rhythm propranolol should be restricted to patients with definite cardiac hyperkinesis and should be used with caution in the presence of underlying heart disease. Patients in congestive heart failure should be given digitalis and diuretic therapy prior to the use of the drug. When a rapid ventricular response associated with atrial fibrillation cannot be adequately controlled with digitalis preparations, the addition of propranolol often will slow the ventricular rate.

Drug complications

The primary actions of β-adrenergic blocking agents can produce detrimental effects. Negative inotropism may cause clinical heart failure in patients with compensated heart disease and may increase overt cardiac failure; this effect can often be prevented or counteracted by the use of digitalis. The antichronotropic action of propranolol and its ability to slow A-V conduction contraindicate the use of this agent in patients with high degrees of A-V block. Propranolol should be used with extreme caution in the presence of first degree heart block or slow sinus rhythm. Since the presence of β-receptor stimulating action is required to maintain normal bronchomotor tone, β-adrenergic blockade is contraindicated in subjects with chronic bronchial asthma. If essential, β-adrenergic blockade should be used carefully in patients with compensated chronic pulmonary disease. The ability to mobilize glucose when necessary is also under β-adrenergic control. Therefore patients with diabetes mellitus who are on insulin or oral antidiabetic agents and may require propranolol must be observed carefully and guided appropriately.

Beta adrenergic blocking agents are effective in the management of the hyperdynamic states, but they must be administered with care and with full knowledge of their potential side effects.

The authors would like to thank Dr. Louis Leiter for his critical review of this manuscript.

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weeks of treatment with this agent to obtain the full antihypertensive effect. The ability of a β adrenergic blocking agent to lower blood pressure in patients with systemic hypertension has been attributed to either readjustment of the baroreceptors or chronic reduction in cardiac output. A centrally mediated tranquilizing effect and a direct anesthetic effect on the peripheral vasculature have also been suggested as mechanisms for its beneficial effects. These actions of propranolol apparently account for the paradoxical response in hypertensive subjects to a drug which elevates peripheral vascular resistance.

In the reported studies oral propranolol alone was administered in doses of 40 to 480 mg daily, beginning slowly with 10 mg three to four times a day and increasing gradually to therapeutic effect or toxicity.

Propranolol has effectively reduced systemic blood pressure in patients with long-standing hypertension as well as those with the earlier milder stages of the disease. However, in the former group there is an absence of a hyperdynamic state and a greater incidence of secondary heart disease. This suggests that in the later stages of systemic hypertension the drug might be less effective and could be associated with a higher incidence of drug complications including congestive heart failure. Therefore propranolol therapy should be restricted to those patients in the earlier labile hyperkinetic phase of the disease.

Hyperkinetic heart syndrome, idiopathic hypertrophic subaortic stenosis, hyperdynamic β adrenergic circulatory state and essential hypertension have been defined as separate entities. However, it is apparent that they have many clinical and hemodynamic findings in common. In all, increased cardiac output has been observed and labile systolic hypertension, decreased peripheral resistance, and increased heart rate may occur. The frequent occurrence of diastolic hypertension in the hyperdynamic β adrenergic circulatory state suggests a link with early essential hypertension.

Some patients with the criteria of hyperkinetic heart syndrome have been shown in our cardiac catheterization laboratory to have idiopathic hypertrophic subaortic stenosis during the application of combined inotropic stimulation. The left ventricular outflow gradient could be demonstrated following a ventricular premature beat or during Valsalva's maneuver while isoproterenol was being infused. The effectiveness of propranolol in ameliorating the manifestations of these hyperkinetic entities is further evidence of a common cardiovascular response either to excess catecholamine stimulation or to exaggerated sensitivity of the β-adrenergic receptor sites of the heart and/or the peripheral vasculature.

Acute dissecting aneurysm of the aorta. Since there is a high mortality rate associated with surgical management of acute dissecting aortic aneurysm, greater emphasis has been placed on medical treatment. Experimental studies and clinical observations have shown that death does not occur with the initial aortic intimal rupture in acute dissection, but is due to the subsequent progressive aortic tear. The kinetics of the aortic pulse wave affect the shearing stress along the aortic wall and, therefore, the progress of the vascular dissection. Medical treatment has been directed toward altering the dynamics of the aortic pulse wave by lowering the blood pressure, decreasing the ejection velocity of blood from the left ventricle, and decreasing the expansile pulse pressure. Ganglionic blocking agents, reserpine, and more recently propranolol have been employed successfully in this medical management. The negative inotropic action of propranolol is of value in reducing the kinetic stresses against the aortic wall. In combination with other antihypertensive agents, propranolol has been successful in the acute and long-term treatment of patients with dissecting aneurysm. Propranolol alone may be used in patients who subsequently become normotensive. The dose range of propranolol employed is 60 to 120 mg per day. Further prolonged observations are needed to fully evaluate the place of propranolol in the management of acute dissecting aortic aneurysm.

Hyperthyroidism. Although thyroid hormone has a direct effect on the cardiovascular system, a significant part of the hyperkinesis results indirectly from interaction with circulating catecholamines. Propranolol frequently will be effective in

reducing the elevated heart rate, mean systolic ejection rate and cardiac output that may be associated with thyrotoxicosis. When indicated as an emergency interim measure propranolol can promptly improve the hyperdynamic cardiovascular manifestations of this metabolic abnormality while awaiting the effects of specific treatment. In the presence of regular sinus rhythm propranolol should be restricted to patients with definite cardiac hyperkinesis and should be used with caution in the presence of underlying heart disease. Patients in congestive heart failure should be given digitalis and diuretic therapy prior to the use of the drug. When a rapid ventricular response associated with atrial fibrillation cannot be adequately controlled with digitalis preparations, the addition of propranolol often will slow the ventricular rate.

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Annotations

Mechanism of the Wenckebach type of atrioventricular block

Wenckebach periods consist of a series of beats which show a progressive lengthening of atrioventricular (A V) conduction time until conduction fails and one ventricular beat drops out. The next beat is conducted its conduction time is the shortest of the set

The usual explanation states that conduction is depressed. A stimulus arrives at the A V node before the latter has fully recovered from the preceding beat. With each subsequent beat the node becomes more fatigued until one stimulus is blocked In the ensuing long diastole recovery of the node takes place, permitting good conduction of the next stimulus.

Scherf in 1929 pointed out that this description does not account for the relatively good conduction afte the block The cells proximal to the block should experience even more fatigue and should not permit the next impulse to even arrive at the site of the block

In this report an explanation is proposed which is based on recent descriptions of the action potential (AP) of A V nodal cells. [7] It describes the interplay of decremental conduction with electrotonic prolongation and shortening of the AP

Conduction along a chain of cells is dependent on the rate and amplitude of the depolarization phase of the AP A slow a d low discharge stimulates the next cell in a sluggish manner The cells of the A V node on the atrial side normally have a relatively slow and low depolarization phase so that conduction here is slow Approaching the His bundle the rate and amplitude of the depolarization increases and conduction accelerates. In health the sum of the conduction rates is stable. Variations of the A V conduction usually due to neurogenic influences are not of the nature of Wenckebach periods The latter are found only in pathologic states where conduction is depressed and delayed.

In nodal tissue exhibiting conduction delay intracellular recordings show decremental conduction.[1,7] A depressed cell has an abnormally low and low depolarization which fires the next cell sluggishly The depolarization phase exhibits a distinctly slow initial step leading into a regenerative spike. As conduction proceeds from cell to cell, the early step formation becomes more pronounced while the regenerative spike ppears later Since the regenerative spike is the chief source of stimulating current for the next cell, the conduction becomes progressively slower along the chain of cells. Finally one cell may develop only the step phase of depolarizations (also called the local or graded response) with failure of the regenerative spike to develop whereupon conduction is blocked. If the depression is not that severe, there is only a delay of conduction.

The second component of the mechanism proposed for the Wenckebach period is the electrotonic lengthening and shortening of the AP

Several groups of investigators[1-4] have shown that there is a distinct influence on a cell's AP by the electrotonic potential of adjacent cells especially when there is a delay of conduction. Mendez and Moe[4] describe this in detail When conduction is depressed, the AP of a cell is prolonged electrotonically by the delayed AP of the cell it stimulated The greater the delay the greater the prolongation of the AP of the firing cell. Conversely when the conduction is blocked that state of polarization of the adjacent cells distal to the block hastens the repolarization of the cells proximal Accordingly the last timulated cell experiences a short AP If conduction is normal there is very little of this effect because the AP of the neighboring cells are so close to each other in time. The refractory period is proportional to the AP Indeed the relative refractory period extends considerably beyond the end of the AP.[8] When conduction is depressed the refractory period as expressed by changes in the duration of the AP is altered by electrotonic effects of adjacent cells.

We can now combine decremental conduction with electrotonic influences on the AP n depressed tissue to generate Wenckebach periods.

The A V conduction time increases with each successive beat during the sequence with the increase greatest n the second beat after the block. Decremental conduction is responsible for some of the progressive increase When an impulse stops at a given boundary and resumes travel after a significant delay the refractory period of the cells distal to the boundary will not be prolonged per se. However in term of propagation of a subsequent impulse the temporal shift is equivalent to an increase of the refractory period.[4] At the same time cells involved in the delay will suffer an electrotonic prolongation of their AP and accordingly of their refractory period Both factors contribute to the progressive delay of the P-R interval

Finally the period ends with a blocked impulse. The AP of the cells proximal to the block will now enjoy a short duration because the adjacent cells, which failed to fire, remain fully polarized and

electrotonically impart their polarization to the cells proximal to block. Accordingly these proximal cells will recover their excitability rapidly. The cells distal to the block will have recovered their excitability by the time the next impulse arrives since they are not depolarized except for a very short, graded response. The stimulus after the block finds recovered tissue in all parts of the formerly depressed area and the A-V conduction is often surprisingly good. This is probably the reason why the marked increase of the conduction time takes place with the beat after the first conducted beat. The first conducted beat enjoys the extra degree of recovery afforded by both the electrotonic shortening of the AP for the cells proximal to the block and the long recovery period for the cells distal. The second beat encounters both factors which increase refractoriness, namely decremental conduction and electrotonic prolongation of the AP.

See Fig. 2 in reference 3. Note that cell N1 shows the effect of electrotonic activity on the repolarization phase. The AP of the blocked impulse shows shorter duration; the depolarization rise of the first conducted beat of the period appears steeper. Cell N2, which is distal to the block, shows progressive delay of the depolarization spike typical of decremental conduction.

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Myocardial infarction with normal selective coronary arteriograms

Coronary arteriography usually correlates well with the clinical diagnosis of myocardial infarction.[1-4] Occasionally the diagnosis of myocardial infarction based on clinical ground, including electrocardiographic and enzyme abnormalities, is not supported by coronary arteriograms which show no obstructive disease.

We have recently reported 6 such examples, selected from 71 patients who had an abnormal electrocardiographic pattern indicative of myocardial infarction in the past or at the time of the study together with an adequately documented clinical history of myocardial infarction and technically satisfactory selective cine coronary arteriograms. It was postulated that coronary emboli which had subsequently undergone lysis had caused the infarction in 3 of these patients, 2 with Starr-Edward mitral prosthesis and one with aortic stenosis in whom the infarction had occurred during retrograde left-heart catheterization. On the basis of the unusual aspect of the left coronary artery noted in 2 other patients, it was suggested that the myocardial infarction in the 3 remaining patients had resulted from coronary thrombosis followed by recanalization.

Such cases frequently become diagnostic problems because of the unexpected normalcy of the coronary arteriograms. The possibility of another disease having simulated myocardial infarction, such as myocarditis, pericarditis, or pulmonary embolism, is then, in retrospective fashion, considered more seriously. Nevertheless true myocardial infarction cannot be excluded entirely in such cases.

The explanations and mechanisms possibly involved in the production of such myocardial infarction without arteriographic obstruction may be summarized as follows:

A. Infarction caused by coronary occlusion not evident on cine coronary arteriograms
   1. Occlusion overlooked
   2. Lysis of thrombus or emboli (recanalization)
   3. Temporary occlusion by functional constriction (spasm)
   4. Pathology of the microcirculation not

B. Infarction not caused by a coronary occlusion
  1. Markedly decreased coronary blood flow
  2. *Oxygen dissociation diffusion and/or* myocardial utilization impairment
  3. Precapillary coronary arteriovenous *shunting*
  4. Nonischemic necrosis.

In fact, coronary artery obstruction may not be identified on the arteriograms and on the other hand it is not the only cause of ischemic heart disease. Undoubtedly cine coronary arteriography has limitations and pitfalls. Present-day techniques do not picture the small intramyocardial arteries. Furthermore, errors of interpretation and underestimation of lesions do occur albeit rarely in experienced hands, particularly when good selective injections are obtained in several projections including the lateral frontal and both oblique views. *Certain types of obstructive lesions however can* not be easily recognized for example an occlusion at the origin of a branch flush with the wall of the mother artery may be overlooked at coronary arteriography unless the resulting abnormal vessel distribution which at times is not easily distinguishable from normal anatomical variants, is correctly interpreted. Although postmortem studies have shown that myocardial infarction is usually associated with severe obstructive lesions *of two to three main coronary arteries, Proudfit,* Shirey and Sones report a high incidence of single artery involvement at cine coronary arteriography in patients who had myocardial infarction without subsequent angina pectoris. Myocardial infarction resulting from an occlusion at the origin of an artery without significant lesions elsewhere may show no evidence of obstructive disease at coronary arteriography. Minor anomalies may also be the only evidence of previous thrombotic occlusion followed by *recanalization occurring at the site of small* arteriosclerotic lesions not recognized at cine coronary arteriography. In fact, it appears that this technique may underestimate structural changes by 20 to 30 per cent and that smaller lesions may not be identified or appear as nonsignificant wall irregularities. Coronary emboli which have produced a myocardial infarction may also undergo lysis and leave no clue whatsoever except for the primary pathology from which they originated. Functional *arterial constriction or coronary spasm* of long duration has been postulated as a primary cause of myocardial infarction,[1] but such unusual vasomotor activity is not generally held responsible for myocardial infarction in humans, although it has been produced experimentally in animals.[11] Obstructive changes of the microcirculation which are not visualized by contemporary techniques do not appear to produce myocardial necrosis of the type associated with the clinical syndrome of myocardial infarction.[12]

In rare cases, myocardial infarction is not produced by obstructive coronary disease. Carbon monoxide poisoning has been reported to produce myocardial ischemia and infarction through failure of the oxygen transport mechanism.[13] Recently Eliot and Bratt[14] have described patients with myocardial infarction in whom *anomalous* hemoglobin-oxygen dissociation curves were found. Other rare causes of myocardial necrosis are myocardial contusion[15] and cardiac vein thrombosis. Coronary arteriovenous shunting resulting in massive myocardial infarction has been produced experimentally in animals. Other mechanisms producing *myocardial necrosis which could simulate* the clinical syndrome of myocardial infarction, such as metabolic, electrolytic, and chemical abnormalities, have been *observed* in experimental animals[7,16] but have not been demonstrated in humans.

Undoubtedly some of these cases of myocardial infarction without obstructive disease at coronary arteriography are not cases of myocardial infarction at all but are unidentified cases of myocarditis, pericarditis pulmonary emboli acute pancreatitis, gastrointestinal disorders, or some other simulating conditions. Electrocardiographic patterns of myo*cardial infarction without its clinical* and laboratory counterparts are also found in other heart disease of which the most frequent are idiopathic myocardiopathies,[9] familial cardiomyopathy,[18] and idiopathic hypertrophic subaortic stenosis. It is only after such possibilities have been excluded that the diagnosis of myocardial infarction without arteriographic evidence of obstructive coronary disease may be seriously considered. A helpful supporting finding is the presence at left ventriculography of an *akinetic wall area in the region* of the infarction as defined by electrocardiography. It may be postulated that the prognosis is possibly better in these cases than that associated with diffuse and severe coronary atherosclerosis. For this reason, and because of possible erroneous clinical diagnosis of myocardial infarction, coronary arteriography appears indicated in all cases of *myocardial infarction* with atypical features or with an inadequately documented clinical history and laboratory findings, particularly in young productive *persons.*

Similarly, seemingly genuine angina pectoris with characteristic electrocardiographic anomalies may have normal or slightly altered coronary arteriograms.[19,20] Again the clinical diagnosis should be seriously reassessed and other possible causes considered before a verdict of ischemic heart disease is given although myocardial ischemia may be produced by mechanisms other than obstructive disease of the coronary arteries visualized by pres*ent-day techniques of coronary* arteriography.

If the lack of definite arteriographic evidence of obstructive coronary disease does not necessarily exclude ischemic heart disease be it myocardial infarction or angina pectoris, a satisfactory explanation of these rare cases is not easily obtained at the present time. Such diagnostic problems which *might not have been suspected before the availa*bility of coronary arteriography will undoubtedly become more frequent. Indeed, these rare cases highlight the necessity of further research related to the pathogenesis of ischemic heart disease.

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Anesthesia dogs and cardiovascular data

The importance of realizing that many so-called "normal" dogs are not normal when attempting to interpret experimental data has been emphasized. Another equally important factor when studying dogs is the influence of the anesthetic, if one is used, on the results. Anesthetics not only modify the circulation but, when combined with pharmacologic compounds or experimental procedures, may produce results not found when unanesthetized dogs are used or when dogs are anesthetized with different agents. These possible variations in results render the interpretation of data difficult and comparisons with data from unanesthetized dogs or from dogs anesthetized with different agents impossible.

B Infarction not caused by a coronary occlusion
1 Markedly decreased coronary blood flow
2 Oxygen dissociation, diffusion, and/or myocardial utilization impairment
3 Precapillary coronary arteriovenous shunting
4 Nonischemic necrosis.

In fact, coronary artery obstruction may not be identified on the arteriograms and on the other hand it is not the only cause of ischemic heart disease. Undoubtedly cine coronary arteriography has limitations and pitfalls. Present-day techniques do not picture the small intramyocardial arteries. Furthermore, errors of interpretation and underestimation of lesions do occur albeit rarely in experienced hands, particularly when good selective injections are obtained in several projections, including the lateral frontal and both oblique views. Certain types of obstructive lesions, however can not be easily recognized for example, an occlusion at the origin of a branch flush with the wall of the mother artery may be overlooked at coronary arteriography unless the resulting abnormal vessel distribution which at times is not easily distinguishable from normal anatomical variants, correctly interpreted. Although postmortem studies [8] have shown that myocardial infarction is usually associated with severe obstructive lesions of two to three main coronary arteries, Proudfit Shirey and Sones[1] report a high incidence of single artery involvement at cine coronary arteriography in patients who had myocardial infarction without subsequent angina pectoris. Myocardial infarction resulting from an occlusion at the origin of an artery without significant lesion elsewhere may show no evidence of obstructive disease at coronary arteriography Minor anomalies may also be the only evidence of previous thrombotic occlusion followed by recanalization, occurring at the site of small arteriosclerotic lesions not recognized at cine coronary arteriography In fact, it appears that this technique may underestimate structural changes by 20 to 30 per cent and that smaller lesions may not be identified or appear as nonsignificant wall irregularities. Coronary emboli which have produced a myocardial infarction may also undergo lysis and leave no clue whatsoever except for the primary pathology from which they originated. Functional arterial constriction or coronary spasm of long duration has been postulated as a primary cause of myocardial infarction, but such unusual vasomotor activity is not generally held responsible for myocardial infarction in humans, although it has been produced experimentally in animals. Obstructive changes of the microcirculation which are not visualized by contemporary techniques do not appear to produce myocardial necrosis of the type associated with the clinical syndrome of myocardial infarction.[u]

In rare cases, myocardial infarction is not produced by obstructive coronary disease Carbon monoxide poisoning has been reported to produce myocardial ischemia and infarction through failure of the oxygen transport mechanism.[u] Recently Eliot and Bratt have described patients with myocardial infarction in whom anomalous hemoglobin-oxygen dissociation curves were found. Other rare causes of myocardial necrosis are myocardial contusion[u] and cardiac vein thrombosis Coronary arteriovenous shunting resulting in massive myocardial infarction has been produced experimentally in animals. Other mechanisms producing myocardial necrosis which could simulate the clinical syndrome of myocardial infarction, such as metabolic, electrolytic and chemical abnormalities, have been observed in experimental animals [u] but have not been demonstrated in humans.

Undoubtedly some of these cases of myocardial infarction without obstructive disease at coronary arteriography are not cases of myocardial infarction at all but are unidentified cases of myocarditis pericarditis, pulmonary emboli acute pancreatitis, gastrointestinal disorders or some other simulating conditions. Electrocardiographic patterns of myocardial infarction without its clinical and laboratory counterparts are also found in other heart diseases of which the most frequent are idiopathic myocardiopathies, familial cardiomyopathy [u] and idiopathic hypertrophic subaortic stenosis.[u] It is only after such possibilities have been excluded that the diagnosis of myocardial infarction without arteriographic evidence of obstructive coronary disease may be seriously considered A helpful supporting finding is the presence at left ventriculography of an akinetic wall area in the region of the infarction as defined by electrocardiography It may be postulated that the prognosis is possibly better in these cases than that associated with diffuse and severe coronary atherosclerosis. For this reason, and because of possible erroneous clinical diagnosis of myocardial infarction coronary arteriography appears indicated in all cases of myocardial infarctions with typical features or with an inadequately documented clinical history and laboratory findings, particularly in young productive persons.

Similarly seemingly genuine angina pectoris with characteristic electrocardiographic anomalies may have normal or slightly altered coronary arteriograms.[u,u] Again the clinical diagnosis should be seriously reassessed and other possible causes considered before a verdict of ischemic heart disease is given, although myocardial ischemia may be produced by mechanisms other than obstructive disease of the coronary arteries visualized by present-day techniques of coronary arteriography

If the lack of definite arteriographic evidence of obstructive coronary disease does not necessarily exclude ischemic heart disease be it myocardial infarction or angina pectoris, a satisfactory explanation of these rare cases is not easily obtained at the present time Such diagnostic problem which might not have been suspected before the availability of coronary arteriography will undoubtedly become more frequent Indeed these rare cases highlight the necessity of further research related to the pathogenesis of ischemic heart disease.

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Why does the electrocardiogram of the dog change with a change in the foreleg position?

The fact that the electrocardiograms (ECG) of normal dogs exhibit considerable variability even in the course of one experiment has been described in the literature for more than 40 years. Ten years ago the workers in our institute described a position for an animal in which the serial electrocardiographic tracings were relatively consistent, if the position was kept unchanged. That was the right lateral recumbent position of the dog with the forelegs in semiflexion (position A). With ventral flexion of the right foreleg and simultaneous dorsal flexion of the left foreleg (position B) the ECG shows leftward shift of the electric axis in standard leads and changes in the repolarization part of the ECG. With ventral flexion of the left foreleg and simultaneous dorsal flexion of the right foreleg (position C) the ECG is changing and exhibits the rightward shift of electric axis and the marked changes in the repolarization part of the ECG.

ECG changes in positions A, B and C were expressed by evaluating the ventricular gradient, the vector ÂQRS and ÂT in the frontal plane, calculated from Leads I and III of the Einthoven system. In comparison with data for position A, statistically significant changes of evaluated vectors have been observed in positions B and C. Later on, a procedure was done on this group of dogs to create adhesions between the heart and the anterior thoracic wall to prevent an eventual change of the heart position resulting from changes in the positions of the limbs. *The ECG changes in dogs in positions B and C were similar to those for the dogs without adhesions.* ECG in both groups also exhibited changes in the precordial Leads V to V and in the unipolar Leads V, V and V in positions B and C.

We used the Grishman system to describe the possible rotation of the heart electric axis in space. Using this lead system no significant changes in both the size and direction of the ventricular gradient as well as in the vectors SÂQRS and SÂT were observed with changes of the limb positions (positions B and C). Due to this fact, we came to the conclusion that using the Einthoven limb leads, the unipolar leads (V, V and V), or the precordial lead (V to V), the ECG was influenced by a change in the position of the forelegs, but was not influenced if the Grishman or McFee systems were used. These facts are explained as follows. With the standard Einthoven leads, a change occurs in the position of the physiologic electrode which is formed by limb insertions to the trunk with change in the position of the forelegs. The observed ECG change is due to the change in the position of the physiologic electrode with respect to the heart. The change in the position of the physiologic electrode represents a change of the lead axis with respect to the representative dipole of the heart. Changes in the unipolar limb and precordial leads are regarded to be due to fluctuation in the potential of the Wilson terminal. Changes in the Einthoven limb leads (the change of the lead axis with respect to the representative dipole of the heart) cause a change in the potential, with respect to the way in which the unipolar limb and precordial leads are recorded. This supposition was verified by placing the electrodes of Wilson terminal on the chest before recording the unipolar precordial leads. In this case only minimal changes occur in the ECG in Leads V to V.

The McFee-Parungao and Grishman systems give well-reproducible results. Using these systems no change occurs in the lead axis with respect to the representative dipole of the heart, with the change in the foreleg position.

Good and reproducible results can be obtained by every system using no limb electrodes or using no recording with respect to the Wilson terminal.

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The most popular anesthetics currently used on dogs by investigators are sodium pentobarbital (or closely related compound) alpha chloralose morphine and urethane (ethyl carbamate) as well as various combinations of these agents. Pentobarbital sodium anesthesia in dogs increases heart rate (presumably through it anticholinergic effect) causes a moderate[1] to marked[2] decrease in cardiac output and a decrease in systemic arterial blood pressure.[2-4] The myocardial depressant effects of barbiturates may involve interference with the ability of the sarcoplasmic reticulum of the myocyte to handle calcium. Alpha chloralose anesthesia in dogs increases heart rate and systemic arterial blood pressure. It decreases stroke volume and left ventricular maximal dp/dt in the dog heart lung preparation and produces a rise in left ventricular end diastolic pressure Autonomic nervous system reflexes are disturbed by chloralose in an unpredictable fashion Morphine alone is seldom used as an anesthetic but when combined with chloralose produces effects similar to those seen with pentobarbital anesthesia with the exception of tachycardia Dogs anesthetized with urethane (ethyl carbamate) have a higher resting cardiac output, pulmonary venous and arterial pressure, and pulmonary blood volume and a lower heart rate than dogs anesthetized with pentobarbital. In rats, urethane and pentobarbital exert different effects on the distribution of peripheral catecholamines which may account for some of their differing effect on cardiovascular responses Prolonged urethane anesthesia in dogs produces a steady decline in systemic and pulmonary blood pressure pulmonary blood volume and cardiac output

As can be seen from the above comments, there is a problem of deciding whether or not the cardiovascular changes recorded during an experiment in dogs are due to pharmacologic agent or experimental procedure being studied or to the anesthetic agent used. However the problem is even more complex, as illustrated by the following recent observations noted by and other investigators. When the effects of prostaglandin E (PGE) on the circulation of intact dogs were studied, different results were obtained depending on whether pentobarbital or urethane was used as the anesthetic. In dogs anesthetized with urethane intra arterial (femoral artery) injection of PGE decreased cardiac output whereas in dogs anesthetized with pentobarbital intra-arterial (femoral artery) injection of PGE increased cardiac output. While studying the immediate hemodynamic effects of acute coronary occlusion it was noted that in dogs anesthetized with chloralose-urethane, the heart rate and systemic blood pressure decreased and the left ventricular end-diastolic pressure increased whereas in dogs anesthetized with chloralose-morphine, the heart rate increased and there was little change in systemic arterial blood pressure or left ventricular end diastolic pressure.[11] In unanesthetized dogs procainamide was found to exert no deleterious hemodynamic effects, whereas the opposite effect was true when procainamide was administered to anesthetized dogs.[12]

It is apparent from this brief discussion that anesthetic agents not only have profound circulatory effects of their own, but will influence the circulatory responses to pharmacologic agents or other factors being studied. Thus, when attempting to interpret cardiovascular data obtained from experiments on anesthetized dogs, it must be remembered that the data may reflect not only the effect on the dog of the pharmacologic agent or procedure under study but also the state of health of the dog The interrelated effects of the anesthetic agent or procedure under study and the unknown state of health of the dog make the interpretation of results and comparison of data among investigators difficult or impossible. This is illustrated by our studies with PGE

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Editorial

The second heart sound in health and in pulmonary hypertension

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Splitting of the second heart sound in the pulmonary area into two components was first recognized by Potain (1866) In expiration the two components *fuse*, while in inspiration delay of pulmonary valve closure (P_2) occurs almost invariably in healthy subjects, enabling identification of aortic valve closure (A_2) and P_2, and hence comparison of the duration of right and left ventricular systole. Knowledge of the splitting of the second sound has proved an essential part of auscultation of the heart, and greatly facilitates the bedside diagnosis of atrial septal defect, pulmonary stenosis, physiologic murmurs, conduction defects, and ventricular function.[3]

A detailed study of the second heart sound (S_2) in normal subjects has been made by several authors[4-] and the main emphasis has been upon an analysis of the splitting of S_2 during respiration into its two components. Though these authors have shown that A becomes earlier and P later at the beginning of inspiration there was disagreement about the relative contribution of each of these events to the width of splitting of S_2. Recently in order to establish normal values, we[8] analyzed the second heart sound by high frequency phonocardiography (which approximated to normal auscultation) in a number of healthy subjects from infancy to old age. The relative intensities of A_2 and P_2 in the pulmonary area, and the frequency of transmission of P to the mitral area received particular attention since in heart disease these characteristics may be altered. Our results have shown that 90 per cent of normal subjects have a single S_2 in the pulmonary area in expiration In agreement with other authors,[10,11] expiratory splitting of greater than 0 02 second (A and P_2 clearly distinguishable on auscultation) was very unusual The degree of inspiratory splitting ranged from 0 02 to 0 06 second but the most important factor determining the degree of inspiratory splitting is the depth of inspiration. While delay of P is the main feature in inspiratory splitting of S_2, the movement of A during respiration has received considerable comment.[11,12] Our findings showed that an average of 29 per cent of the splitting of S_2 was due to an early A in inspiration which is in agreement with the view of Aygen and Braunwald[7] However in 19 per cent of normal subjects there was no detectable movement of A_2 at all and this was particularly true of the subjects in the 40 to 80 age group.

The relative intensity of A_2 and P in the pulmonary area was also studied[8] and in 94 per cent of all age groups A is louder than P_2, and we found only 3 instances of P being louder than A in the pulmonary

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Book reviews

PRACTICAL EVALUATION OF THE ELECTROCARDIOGRAM A Synopsis of Differential Diagnosis By R Schroeder M D and H Suedhof M D Springfield, Ill. 1969 Charles C Thomas Publisher 104 pages. Price $19 75

This brief outline of the characteristics of normal and abnormal electrocardiograms is well planned and clearly and accurately presented. This guide can be helpful to those beginning to learn electrocardiography The authors present their data mainly in diagrams and tables which are simple and well organized. Surely the entire field of electrocardiography cannot be presented in less than 100 pages, but the text and the accompanying manual of 151 actual electrocardiograms provide material of considerable value in learning to understand and read electrocardiograms. This book is recommended to beginners

HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY A Clinical Study By I S. Meerschwam Amsterdam, 1969 Excerpta Medica Foundation 206 pages. Price $14.50

Dr Meerschwam has adequately summarized the essentials of hypertrophic obstructive cardiomyopathy The presentation is for the clinician The subject is presented in a conventional fashion, viz., history symptomatology physical signs, and roentgenologic, electrocardiographic phonocardiographic, and hemodynamic manifestations. The references are complete and the index detailed This is a very good monograph on this disease It is highly recommended to those who wish to review important and practical information on this disease

ABC OF THE ECG A Guide to Electrocardiography By J Boutkan M D Springfield, Ill. 1969 Charles C Thomas Publisher 204 pages. Price $8 00

Dr Boutkan has written a simple guide to electrocardiography for beginners and busy physicians who have not had time to study the subject thoroughly This is a good manual which is supported in the first part of the book by aspects of the theory of electrocardiography whereas the major portion consists of excellent tracings with interpretations. The author has done a good job However to appreciate the material adequately the reader must have a knowledge of the fundamental principles of electrocardiography and electrophysiology as now accepted. Without this knowledge, the reader will not understand fully the discussions and tracings presented. Nevertheless, this brief guide is a good one. It is accurate, lucid, and well planned The guide should be useful to beginners and busy physicians.

DIAGNOSTIC ELECTROCARDIOGRAPHY By Michael C. Ritota, M D D.Sc., Philadelphia and Toronto, 1969 J B Lippincott Company 174 pages. Price $15 00

Dr Ritota has written a compendium consisting of representative commonly encountered electrocardiograms with his interpretations. The atlas of tracings is not significantly different from the many manuals of this sort already available The tracings are clear well labelled, and well selected This compendium of actual recordings can be useful to those who do not already know how to interpret the most common electrocardiograms.

ELECTROPHYSIOLOGY OF PACING AND CARDIOVERSION By Augustin Castellanos, Jr M D and Louis Lemberg M D New York, 1969 Appleton-Century Crofts Inc. Educational Division, Meredith Corporation, 250 pages. Price $12.00.

Drs. Castellanos and Lemberg have written a useful and timely book. The use of pacing in cardiology is increasing constantly Cardioversion, likewise is being employed in more and more hospitals around the world. The authors summarize in this monograph their thoughts and practices, most of which have been published elsewhere. The reader may wish to study the original papers to learn detail of their techniques. For example on p. 171 they refer to the method of Linenthal and Zoll for measuring conduction time but fail to describe it The illustrations and diagrams are clear and the legends adequate A bibliography is appended to each chapter The description of electric cardioversion is adequate and the common arrhythmias associated with cardioversion are discussed. This is a useful book. A background in electrocardiography is necessary for full appreciation of the book however

ELECTROCARDIOGRAMS A Systematic Method of Reading Them By Michael I Armstrong M B., B.S. Baltimore, 1968 The William & Wilkins Company 76 pages. Price $7.50.

In 73 pages, Dr Armstrong summarizes a study of electrocardiography This is done very well and clearly The book presents a course in electrocardiography in an empirical manner There is practically no discussion of the principles of electrocardiography or electrophysiology These the reader must obtain elsewhere preferably before he reads this book. Unfortunately some of the minimal essential mechanisms which are accepted to explain ECG patterns and disorders of rhythm are not adequately discussed. Such knowledge is essential for a satisfactory understanding and interpretation of the ECG This small book is accurate and useful for those who wish to interpret the ECG from an empirical point of view

in wide splitting of the second heart sound but P always remains accentuated Careful analysis of the second heart sound after banding has been extremely useful in assessing whether the pulmonary vascular resistance is continuing to rise or fall. A clinical improvement in these infants may occur because the pulmonary flow has been diminished by the banding procedure or by a continuing rise of the pulmonary vascular resistance (Eisenmenger situation) and repeated cardiac catheter studies may be necessary to resolve this problem However splitting of the second heart sound in expi ration decreases and eventually S_2 becomes single when the pulmonary vascular resist ance continues to rise despite satisfactory banding of the pulmonary artery When banding results in a reduction of pulmonary flow leading to a halt in the rise or even a fall of the pulmonary vascular resistance S_2 remains widely split or may even in crease and the intensity of P diminishes, since the pulmonary stenosis increases as the infant grows. Serial analysis of S_2 is therefore a valuable method of following the clinical progress of these infants and reduces the need for repeated cardiac catheterization.

In patients with primary pulmonary hypertension or chronic respiratory disease with pulmonary hypertension the second heart sound is usually split by 0 02 second or more in experation (without right bundle branch block) a finding which is present in only 2 per cent of normal subjects. This implies that right ventricular systole is prolonged perhaps as a result of right ventricular dysfunction [18] In insp ration A remains fixed and P increases in most patients. Occasionally P also remains con stant so that the split of S_2 is fixed" throughout respiration indicating that right ventricular ejection cannot be prolonged in response to an increased systolic volume load on inspiration

Since A is larger than P in the pulmonary area in 94 per cent of normal subjects, equality or A less than P usually means an abnormally increased intensity of P_2, and indicates an atrial septal defect (nor motensive or hypertensive) or pulmonary hypertension and this physical sign is sel dom absent in these two situations. Transmission of P to the mitral area is an even more certain abnormality (except in in fants) though it does not differentiate normotensive from hypertensive atrial septal defects and is surprisingly infrequent in mitral valve disease. In normotensive or hypertensive atrial septal defect the right ventricle is subjected to a volume overload and is therefore greatly dilated it is lying anteriorly and seems to form the apex of the heart more frequently than with right ventricular hypertrophy from pressure overload. This right ventricular apex in atrial septal defect probably accounts in part for the audibility of P in the mitral area, but another factor is a true increase in intensity of P even in a normotensive atrial septal defect, since P was louder than A_2 in the pulmonary area in the majority of cases. This raises the question of the increased intensity of P_2. While the dilated main pulmonary artery of normotensive atrial septal defect may be a factor in bringing the sound nearer to the chest wall, the large pulse pressure in the main pulmonary artery of atrial septal defect, related to the increased stroke volume of the right ventricle may increase the veloc ty with which the pulmonary valve closes. Indeed an increased rate of closure of the pulmonary valve from a wide pulse pressure in the pulmonary artery may be a more important factor in accentuating P than increased pressure of tself and pre sumably in pulmonary vascular disease there is increased rigidity of the pulmonary vascular system which is likely to cause a sharp pulse.

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area in normal healthy subjects and they were under 15 years of age. In adults when P_2 is louder than A_2 in the pulmonary area the possibility of pulmonary hypertension should be considered Since several factors may result in the transmission of P_2 to the mitral area such as pulmonary hypertension or right ventricular enlargement the presence or absence of P_2 in the mitral area was also studied in normal subjects We found that P_2 was present in the mitral area in 6 per cent of normal subjects and all were under 15 years of age.[8] This is perhaps not surprising when the proximity of the pulmonary and mitral areas in children is considered Moreover in the rare instances in children when P_2 was louder than A_2 in the pulmonary area P_2 could be heard in the mitral area

The characteristics of the second heart sound both in the relative intensity of its components and their behavior during inspiration are worthy of close attention during routine auscultation for a change in their character may be the earliest clinical sign of pulmonary hypertension Other clinical signs of pulmonary hypertension such as atrial systolic waves in the venous pulse may be inconsistent abnormal right ventricular movement may be absorbed by the chest wall or confused with systolic expansion of the left atrium ejection sounds may be aortic rather than pulmonary Electrocardiographic changes are late or may be concealed by left ventricular hypertrophy and radiologic changes may be absent. Wood[11] stated that the second heart sound in pulmonary hypertension was abnormally closely split with accentuation of the pulmonary component a view still currently widely held however recently we have found[9] that though this may be correct in certain situations no such generalization can be made We studied 167 patients with proven pulmonary hypertension due to a variety of causes, rheumatic mitral valve disease, atrial septal defect, ventricular septal defect and patent ductus arteriosus, and primary pulmonary hypertension and a few patients with chronic respiratory disease.

Abnormally close splitting of the second heart sound was shown to apply only to a large ventricular septal defect or single ventricle and even then the pulmonary vascular resistance had to be raised to systemic levels The auscultatory illusion of abnormally close splitting of S_2 in the pulmonary area may have been created by the difficulty in hearing the relatively soft A_2 preceding the greatly accentuated P_2 found in many cases of pulmonary hypertension though the two sounds, A_2 and P_2 can usually be easily heard at the mitral area where they are often of equal intensity

Inspiratory increase in the separation of the two components of the second sound is the rule in pulmonary hypertension without right ventricular failure (except with an interatrial communication or Eisenmenger ventricular septal defect) and it is due to inspiratory delay in P_2 as in normal subjects. However the usual respiratory movement of A_2 seen on the phonocardiogram was absent in patients with pulmonary hypertension due to mitral valve disease, ventricular septal defects and patent ductus arteriosus Despite the lack of help from abnormalities of splitting of the second sound in diagnosing pulmonary hypertension except in Eisenmenger ventricular septal defects with and without patent ductus arteriosus where S_2 is single the inspiratory separation of the two components not only allows a comparison of relative intensity but also permits a comparison of the duration of systole of the right and left ventricle in the same heart cycle. Furthermore the detection of differences in splitting of the second heart sound remains the only clinical way of differentiating Eisenmenger atrial septal defect, ventricular septal defect, and patent ductus arteriosus. Wide fixed splitting is retained in the Eisenmenger atrial septal defect (both A_2 and P_2 delay on inspiration) S_2 becomes single with the Eisenmenger ventricular septal defect (fused A_2 and P_2 delay on inspiration) and is physiologic (but A_2 is fixed) with the Eisenmenger patent ductus arteriosus. In pulmonary hypertensive ventricular septal defect, clear separation of the two components of the second sound excludes an Eisenmenger situation and suggests that surgical closure of the defect may be beneficial

Banding of the pulmonary artery in early infancy which is the palliative treatment for a large left to-right shunting ventricular septal defect with failure to thrive results

in wide splitting of the second heart sound but P_2 always remains accentuated. Careful analysis of the second heart sound after banding has been extremely useful in assessing whether the pulmonary vascular resistance is continuing to rise or fall. A clinical improvement in these infants may occur because the pulmonary flow has been diminished by the banding procedure or by a continuing rise of the pulmonary vascular resistance (Eisenmenger situation) and repeated cardiac catheter studies may be necessary to resolve this problem. However splitting of the second heart sound in expiration decreases and eventually S_2 becomes single when the pulmonary vascular resistance continues to rise despite satisfactory banding of the pulmonary artery. When banding results in a reduction of pulmonary flow leading to a halt in the rise or even a fall of the pulmonary vascular resistance S_2 remains widely split or may even increase and the intensity of P_2 diminishes since the pulmonary stenosis increases as the infant grows. Serial analysis of S_2 is therefore a valuable method of following the clinical progress of these infants and reduces the need for repeated cardiac catheterization.

In patients with primary pulmonary hypertension or chronic respiratory disease with pulmonary hypertension the second heart sound is usually split by 0.02 second or more in expiration (without right bundle branch block), a finding which is present in only 2 per cent of normal subjects. This implies that right ventricular systole is prolonged, perhaps as a result of right ventricular dysfunction.[14] In inspiration A_2 remains fixed and P_2 increases in most patients. Occasionally P_2 also remains constant so that the split of S_2 is fixed throughout respiration indicating that right ventricular ejection cannot be prolonged in response to an increased systolic volume load on inspiration.

Since A_2 is larger than P_2 in the pulmonary area in 94 per cent of normal subjects, equality or A_2 less than P_2 usually means an abnormally increased intensity of P_2, and indicates an atrial septal defect (normotensive or hypertensive) or pulmonary hypertension and this physical sign is seldom absent in these two situations. Transmission of P_2 to the mitral area is an even more certain abnormality (except in infants) though it does not differentiate normotensive from hypertensive atrial septal defects and is surprisingly infrequent in mitral valve disease. In normotensive or hypertensive atrial septal defect the right ventricle is subjected to a volume overload and is therefore greatly dilated; it is lying anteriorly and seems to form the apex of the heart more frequently than with right ventricular hypertrophy from pressure overload. This right ventricular apex in atrial septal defect probably accounts in part for the audibility of P_2 in the mitral area, but another factor is a true increase in intensity of P_2 even in a normotensive atrial septal defect, since P_2 was louder than A_2 in the pulmonary area in the majority of cases. This raises the question of the increased intensity of P_2. While the dilated main pulmonary artery of normotensive atrial septal defect may be a factor in bringing the sound nearer to the chest wall, the large pulse pressure in the main pulmonary artery of atrial septal defect, related to the increased stroke volume of the right ventricle, may increase the velocity with which the pulmonary valve closes. Indeed, an increased rate of closure of the pulmonary valve from a wide pulse pressure in the pulmonary artery may be a more important factor in accentuating P_2 than increased pressure of itself, and presumably in pulmonary vascular disease there is increased rigidity of the pulmonary vascular system which is likely to cause a sharp pulse.

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Clinical communications

Vectorcardiogram past forty

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For the vectorcardiogram (VCG) to have value in patients over forty depends upon the reader's ability to discriminate between a VCG typical of the normal population and one containing the special cardiac problems found in this age group. The majority of older patients will have left ventricular enlargement or ischemic heart disease. The reader must, of course, first establish a normal range. When selecting patients for such a compilation, those with pulmonary problems or mechanical overload of the left ventricle can usually be excluded by various means, but those with clinically silent scarring can never be absolutely eliminated. The use of criteria derived from young adults would largely circumvent this problem but may not be justifiable since aging alone probably causes changes in the electrocardiogram (ECG). This study is an attempt to define quantitatively the variations in the VCG of a group over forty years of age in whom every effort was made to exclude heart disease or other factors which influence the VCG. Helm's system of recording with sponge electrodes was utilized. It already has been used extensively in children and younger adults[1,2] and these studies afford a basis for comparison so that the influence of age can be identified on recordings obtained from electrodes integrating surface potentials from large areas (unlike Frank, Cube or older systems).

Patients, measurements, and data analysis

Criteria for selection of patients were similar to those employed in assembling the 133 young adults previously studied.[2] The current series, therefore, is considered an extension of the first so that the influence of age might be examined in a population exceeding 200 persons. This sample size should be sufficient to randomize the effect of certain other constitutional variables such as height and weight since no subjects who were grossly over or under weight were included. Seventy-five Caucasians, mostly hospital staff, were selected as "normal" on the basis of x-rays, hemograms, physical examination, history, and an ECG lacking the features of overt bundle branch block or healed infarction. None had systolic and diastolic blood pressures in excess of 140 and 90 mm. Hg, respectively. Age range was 40 to 99 (mean 51.2 ± 11.3); 84 per cent were between 40 and 60, and 70 per cent were male.

Vectorcardiograms and scalar leads X, Y, and Z were transcribed (Electronics for Medicine) in frontal, horizontal, and right sagittal planes (fp, hp, and sp). Anterior

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and left axillary electrodes were composed of large porous plastic sponges ¼ inch thick (DuPont) moistened with concentrated saline ordinary limb electrodes were applied to the left leg right axilla back and neck[3,4] P and T loop were usually deleted electronically to clarify initial forces since only QRS was analyzed Transcription was interrupted every 4 msec

Morphological divisions of the loops were quantitated after identifying their major changes in direction (greater than 75 degrees in two or more planes)[2,5,7] Vectors at five points were measured *Q is the first,* R is the most leftward point S is the first change past R M is the maximum vector in each plane and lastly the 20 msec vector useful in the diagnosis of myocardial infarction was described By identifying the time at which a major change in direction takes place in two planes the same vector can be located on the third by similar timing and projections on the X Y and Z coordinates even though no directional shift is evident in that plane Two examples of this situation are the R (most leftward) vector in the sp and a Q (initial) vector oriented directly anterior and therefore not visible on the fp Mensuration of this type shows similar or less variance than that of timed consecutive vectors.[7]

Their voltage and position on each plane were noted (R_{fp} R_{hp} etc.) as well as three dimensional or spatial voltage (Q_1 R_1, etc.) calculated by a Pythagorean nomogram.[1] The spatial value for M was computed by determining the spatial value of the largest vector found in any plane Angles were recorded on Helm s reference system[8] The timing of each vector total QRS duration of anterior and of initial superior forces, and the S loop time from the S point to the end of the QRS was determined as *well as the major deflections of the* X Y and Z leads. The rotation clockwise (CW) or counterclockwise (CCW) around Q R and S points was also described wherever possible

Data were analyzed by standard computer programs. For all parameters, mean standard deviation and test for normality of distribution were performed The values for males were compared with those for females (t tests) Data were then compared item by item with those from previously reported young adults with an age range of 16 to 34 (t tests)[2] Finally variance ratios were used to compare the variability of angular position of each planar vector

Table I *Quantitative data on normal QRS loops subjects age 40 to 99*

Variable	Q	20 msec.	R	S	M
Angles (degrees)					
fp	175 ± 58 (75–270)	56 ± 65 (0–215)	35 ± 14 (10– 60)	190 ± 95 (10–350)	36 ± 14 (12– 55)
hp	118 ± 24 (65–160)	65 ± 25 (20–120)	7 ± 17 (360– 37)	269 ± 23 (235–310)	1 3 ± 38 (285– 37)*
sp	359 ± 33 (305– 60)	25 ± 21 (350– 65)	81 ± 26 (32–133)	177 ± 29 (125–225)	108 ± 51 (50–210)
Voltage (mv)					
fp	14 ± 06 (1 3)	33 ± 18 (1 8)	1 6 ± 39 (0 9–2 2)	31 ± 18 (0– 8)	1 6 ± 38 (1 0–2 2)
hp	20 ± 00 (1 4)	35 ± 13 (1 6)	1 4 ± 36 (8–2 1)	58 ± 23 (3–1 1)	1 4 ± 35 (8–2 1)
sp	18 ± 06 (1 3)	33 ± 17 (2 8)	1 0 ± 40 (4–1 8)	64 ± 28 (3–1 2)	1 1 ± 33 (7 1 8)
Spatial	23 ± 08 (1 4)	45 ± 23 (2–1 0)*	1 7 ± 37 (1 1 2 3)	65 ± 26 (3–1 1)	1 7 ± 33 (1 1 2 3)
Timing (msec.)	11 ± 3 (8–16)		40 ± 5 (33–51)	61 ± 8 (50–76)	
	Ant. duration = 42 ± 9 (26–56)		Total QRS = 89 ± 10 (68–110)		
	Initial sup. dur = 9 ± 9 (0–22)		S loop dur = 23 ± 9 (14–43)		
Voltage in orthogonal leads (mv.)					
X	R = 1 3 ± 35 (7 1 9)		S = 13 ± 15 (0– 5)		
Y	R = 84 ± 29 (3–1 6)		S = 19 ± 24 (0– 5)		
Z	R = 46 ± .23 (.2– 9)*		S = 62 ± 26 (3–1 2)*		
		R_z + S = 1 9 ± 42 (1 1 2 7)			

*Nongaussian distribution range = 95 per cent of observations.

with that of the younger patients and coefficients of variation of the voltage measurements were calculated for a similar comparison Coefficients of correlation were calculated between age and all measurements for the pooled data from both groups

Results

Table I contains the statistical description of the data for the older population The ranges quoted encompass 95 per cent of observations and approximate two standard deviations when distribution is normal. Fig 1 compares loops constructed from mean data for children young adults, and older adults.

Table II indicates that there are distinct differences between the men and the women. Most of the timing measurements are less in the female, and the average position of the R_{hp} is 10 degrees less anterior Except for S sex differences in spatial voltage noted in young adults and in pooled data for both series, were not found but several measurements reflected that the posterior deflections of the loop (S vector) were generally smaller in females. In considering normal ranges more precisely than in Table I these items might be stratified by sex, but the number of females is small

Table III shows that the basic difference

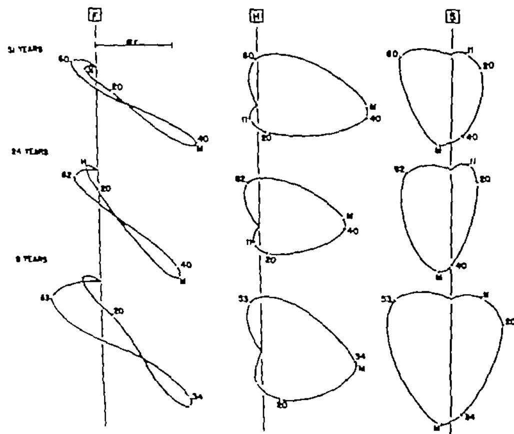


Fig 1 Loops constructed from verage aloes for normal patients. A 1 mv standard common to all loops is at the upper left. The mean age for each group is indicated on the left; there was no overlap in ages. The digits refer to the timing (msec.) for Q, 20 msec., R and S vectors and indicate direction of the transcription. The maximum ector M in each plane, is also noted. The main differences are obvious. The voltage of all vectors of the eight year group is clearly higher than that of the young adults but positions are practically identical. The older adults showed more leftward loop in the fp, a larger projection in the lp and smaller one in the sp. Spatial voltage of Q, R S, and M were statistically indistinguishable and that of the 20 msec. ector slightly larger in the older patients ($p < 0.05$).

Table II *Significant differences between sexes subjects age 40 to 99*

Variables	Females Mean (S D)	Males Mean (S D)	t	p<
Time (msec.)				
R	38 (5)	41 (5)	−2 65	05
S	57 (6)	62 (8)	−2 62	05
QRS	81 (8)	92 (9)	−4 73	001
Anterior duration	37 (8)	44 (9)	−3 00	01
S-loop duration	24 (6)	30 (10)	−2 56	05
Angle (degrees)				
R_h	0 (14)	10 (17)	−2 50	05
Voltage (mv)				
S_f	22 (16)	35 (17)	−3 04	01
S_h	49 (19)	62 (27)	−2 17	05
S_{sp}	51 (22)	69 (29)	−2 58	05
S_s	53 (22)	70 (26)	−2 74	01
R	36 (16)	50 (25)	−2 33	05

Table III *Significant differences between old and young adults*

Variables	Old adults Mean (S.D)	Young adults Mean (S.D)	t	p<
Initial superior (msec.)	9 (9)	12 (8)	−2 37	05
Angles (degrees)				
Q_{fp}	175 (58)	198 (69)	−2 43	05
20 msec.$_{fp}$	56 (58)	93 (85)	−3 36	001
R_{fp}	35 (14)	50 (13)	−7 86	001
S_{fp}	190 (95)	164 (74)	2 24	05
M_{fp}	36 (14)	51 (19)	−6 21	001
Q_{hp}	118 (24)	108 (26)	2 73	01
R_{hp}	7 (17)	0 (16)	2 67	01
S_{hp}	269 (23)	252 (33)	3 88	001
R_{sp}	81 (26)	90 (20)	−2 82	01
Voltage (mv)				
20 msec.$_{fp}$	33 (18)	24 (17)	3 73	001
R_{hp}	1 4 (36)	1 1 (41)	5 59	001
M_{hp}	1 4 (37)	1 1 (37)	5 03	001
Q_{sp}	18 (08)	21 (12)	−2 07	05
R_{sp}	1 0 (40)	1 24 (41)	−3 54	001
S_{sp}	64 (28)	56 (28)	1 99	05
M_{sp}	1 1 (32)	1 34 (40)	−4 45	001
20_s	45 (23)	38 (17)	2 34	05
R/Q ratio$_{sp}$	8 4 (4 2)	6 6 (3 7)	3 26	05
R	1 3 (35)	1 08 (42)	4 28	001
R	84 (38)	1 2 (46)	−6 31	001
S	62 (26)	52 (26)	2 52	05
Sum R + S	1 94 (42)	1 60 (49)	5 10	001
Q_t	23 (08)	22 (13)	0 48	N.S.
R	1 68 (37)	1 65 (50)	0 50	N.S.
S_t	65 (26)	60 (29)	1 37	N.S.
M	1 67 (38)	1 73 (46)	−0 96	N.S.

N.S., Not significant (p >.10)

from the young adults was the more leftward direction of the loop$_{fp}$. This, however generates numerous secondary differences in individual planar measurements and suggests, therefore, no systematic alteration of configuration. In the fp Q becomes more inferior and 20 R and S become more superior Duration of initial superior forces diminishes. The projection of spatial R and M on the hp is larger There are no detectable differences in the *spatial* voltage of the major vectors. Pooled

Table IV Comparison of variability between old (o) and young (y) adults

Variables	Angles			Voltage	
	SD	SD	F	CV	CV
Q					
fp	58	69	1 41	45	64
hp	24	26	1 17	46	55
sp	33	32	1 06	45	57
spatial	—	—	—	37	59
20 msec.					
fp	58	85	2 14	54	72
hp	25	34	1 84	38	38
sp	21	37	3 10*	46	38
spatial	—	—	—	51	40
R					
fp	14	14	1 00	25	21
hp	17	16	1 12	26	26
sp	26	20	1 69	38	28
spatial	—	—	—	22	21
S					
fp	95	74	1 64	56	64
hp	23	24	1 08	44	45
sp	28	33	1 38	44	46
spatial	—	—	—	40	44
M					
fp	14	21	2 25	23	21
hp	28	57	4 14	27	22
sp	51	30	2 89*	29	26
spatial	—	—	—	23	27

F = variance (larger S.D./smaller S.D.)^2
CV = coefficient of variation (S.D./mean × 100)
*F significant ($p < .01$); others not significant ($p > .05$)

Table V Rotation of loops at Q R, and S points (percentages)

Direction	FP			HP			SP		
	Q	R	S	Q	R	S	Q	R	S
Clockwise	32	49	50	0	5	8	92	89	89
Counterclockwise	51	47	43	99	95	89	3	8	8
Indeterminate	16	4	7	1	0	3	5	3	3

data from both age groups (208 patients between 18 and 99 years) show confirmatory linear correlations of age with the same parameters ($p < 0.01$-0.001) but again no correlation with spatial voltages.

Table IV points out that the VCG for older patients is in some respects less variable than that of young adults. The position of the 20 msec. and M vector shows considerably less scatter. The voltage of Q is also more stable but there is little difference in comparative variance of other voltages.

Table V lists the directional characteristics for Q, R, and S phases of each loop. The percentage of initial CCW rotation around the Q_{fp} is nearly twice as frequent as in the young adults and is also a function of the more leftward loops.

Discussion

Studies with the Frank system also indicate a gradual superior shift of the loops with age,[9, 11] a decrease in variability of the position of the M vector in all planes,[9] and no change in QRS duration.[11] There are some inconsistencies in the reports concerning changes in shape of the loop$_{hp}$, but most state that loops become more posterior.[10, 13] There are some discrepancies found concerning maximum voltage in hp,[13, 14] but most report a clear-cut stepwise

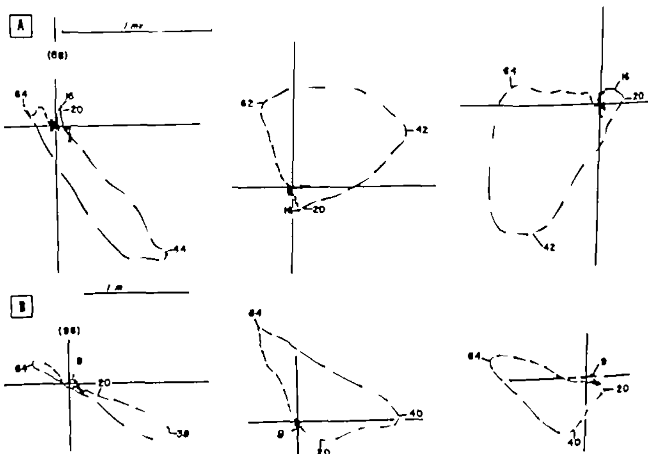


Fig. 2. In this and subsequent figures, 1 mv. calibrations are at the upper left, direction is indicated by the sharp edge of the dash, and interruptions are every 4 msec. From left to right are fp, hp, and sp. Q, 20, R, and S vectors are identified by digits indicating the time in msec. from the beginning of the loop. P and T loops are partially deleted.

These sets were selected to illustrate leftward initial forces. Normal Q waves were absent from left-sided ECG leads. *A* represents a type more often seen in young women, i.e., a vertical clockwise loop$_{fp}$. *B* is different in that the loop$_f$ is nearly horizontal. With this position, Q is ordinarily to the right and rotation CCW. None of this type was seen in young adults.

The loops have other features worth noting. Both are dominantly posterior—*A* because the anterior inscription time is short (29 msec.), and *B* because vector S_{hp} is larger than R_{hp}. In *B* the fortuitous position of S_{fp} causes the ECG pattern of S_1, S_2, S_3. Its size, relative to R, suggests acquired right ventricular disease, but absolute voltage values are comfortably within the normal range.

decrease with age in spatial, as well as individual planar voltages.[11,12,16]

Studies in our laboratory indicate a highly significant correlation ($p < 0.001$) between maximum voltage (Helm) and left ventricular weight, calculated by an angiographic technique and corrected for body surface area, in a large series of adults with under- and overloaded left ventricles.[1] It is interesting therefore to see if voltage by either the Frank or Helm systems follow the corrected heart weights expected at different ages in the normal population.

Although the influence of age on heart weight in the normal population has not been studied definitively, children may have relatively larger hearts. Gasul and associates[17] state that past one year their

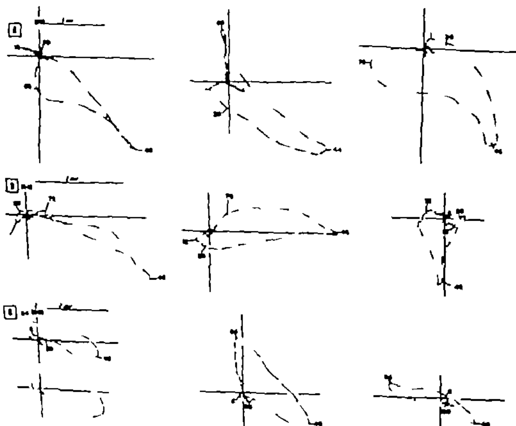


Fig. 2. Loops selected primarily to show criteria suggestive of myocardial infarction or left ventricular hypertrophy. *A*, With R at 40 degrees, Q is nearly in the opposite direction (about 180 degrees), rotation about Q is CW and the configuration is not remarkable. The initial superior forces (22 msec.), however are at the upper limits of normal. If R are more horizontal, and initial superior forces exceeded 24 msec., the initial forces would suggest inferior infarction. Loop is also unusually anterior because of the position of R and the segment between R and S, but, on the basis of the present study is not sufficient evidence for diagnosing posterior myocardial infarction. A brief reversal of transcription occurs at S; this is common when the angle between R and S is acute and not evidence for incomplete right bundle branch block. *B*, Q, rotation is again clockwise, with R at 25 degrees. This combination overlaps with cases of proven inferior wall infarction. Q, however is directed inferiorly and the early superior forces are of short duration (6 to 10 msec.) and not truly initial. The configuration suggests left ventricular hypertrophy but voltages are normal. *C*, Two loops taken a few seconds apart are illustrated. R is at 12 degrees. The rotation of Q is CW in one, CCW in the other. The scalar trace of lead Y showed variation, probably respiratory in QRS, with initial portion being either positive or slightly negative.

One type of VCG in which the ECG exhibits left axis deviation is also illustrated, i.e., horizontal R with CCW rotation. This combination also frequently results in an unusual (CCW) rotation of the loop, which is sometimes considered evidence of inferior apical infarction.

hearts comprise 0 50 per cent of body weight while Gould[18] quotes figures for adults as 0 43 per cent (males) and 0 40 per cent (females) and no change in adults on the basis of age alone Other studies also indicate relatively smaller hearts in females.[19] Helm maximum voltages seem to follow this trend with higher voltages in children,[3] no change in the aging adult and smaller voltages in at least the young adult females. Frank values do so only partially Maximum voltages are also smaller in females[9,10,20] but differ little between children and young adults[21,22] and diminish with age

It is rather extraordinary that maximum voltages (Helm) seem to follow corrected rather than absolute heart weights. The magnitude of body surface potential is, however influenced in a complex manner by extracardiac conduction If heart size (and dipole moment) remained constant in the aging adult this would be the most important determinant. The maximum spatial vector derived from surface leads should be inversely proportional to torso size[23] Increased torso size which would tend do diminish surface potential might also be expected to diminish the effect of the finite boundary of the torso which increases current density at the surface.[24] Changes in angle of curvature of the thoracic wall and a shift in dipole position might also influence surface voltage These

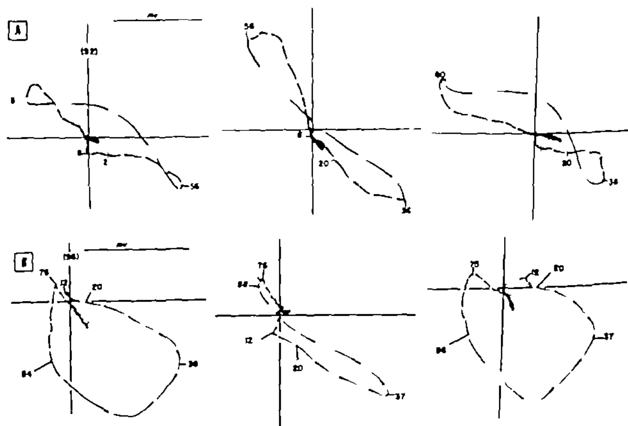


Fig 4 Two examples of unusual configurations due to the relative positions of the major vectors or of the orientation of the loops relative to the arbitrary planes in which they are recorded. *A* Figure eight loops in all three planes principally resulting from unusually wide angles between the major vectors, each of which is at the outer limits of normal distribution. A second type of LAD on the ECG is illustrated. R_f, is in normal position as is S_{fa} but S_{fa} is *unusually* far to the right so that S_f, is very large. The connection between R and S_f is superior and the mean direction is therefore above 0 degrees. Note that as in the other type of LAD (Fig 3 C) the loop is mostly CCW *There are also practically no posterior leftward forces* (cf Fig 3 A). *B* The loops are unusually open so that loop is seen on edge which creates a tendency toward a complex configuration. The wide angle between R and S_{fa} also *contribute to the possibility of a reversal of direction at the S point.* Rotation around S is completely CW The absence of posterior leftward forces is again noteworthy. There are two vectors (S and S') identified in the terminal portion of the loop at approximately 54 and 76 msec. This variant occurs in about 15 per cent of records.

factors probably change with age and should affect surface potential most when sampled by a nonorthogonal lead system such as the standard ECG In the Frank VCG the small number of sampling points, fixed corrective resistances and the uncertainty of the vertical level of the cardiac dipole might cause it to be more sensitive to these distortions than other systems which integrate potentials over large areas of torso. A semigrid system, that of McFee and Parungao also shows higher voltages in children. The reasons for this in spite of what must be the smaller source potential of the smaller hearts, have been reviewed.[38] The sponge electrode is only one of several practical grids currently available for recording the VCG

The normal range of patterns cannot be satisfactorily displayed by a statistical description of single vectors for patterns are created by the relationship of the major vectors to each other as well as by their individual characteristics. If the value of only one vector is near an extreme of the normal range, an unusual relationship will exist with other normal vectors and a pattern variant will occur which will sometimes suggest disease. Since clinical interpretation is usually done by inspection and a few simple measurements, description of this series would be incomplete without illustrating such examples. They were selected principally with the problem of diagnosing left ventricular enlargement (LVH) or myocardial infarction in mind It is not the purpose of this communication to review the extensive criteria published for this purpose but to point out qualifications or cautions in the use of some of them. On the other hand uncertainty remains as to whether those suggesting myocardial scarring are truly normal variants.

Fig 2 illustrates leftward initial forces expressed electrocardiographically by absence of the normal septal Q in left-sided leads. Type A is clearly positional and not infrequent in young adults, particularly females. Type B was found four times in this series but never in our study of young adults. It is presumably a result of isolated septal scarring and/or incomplete left bun

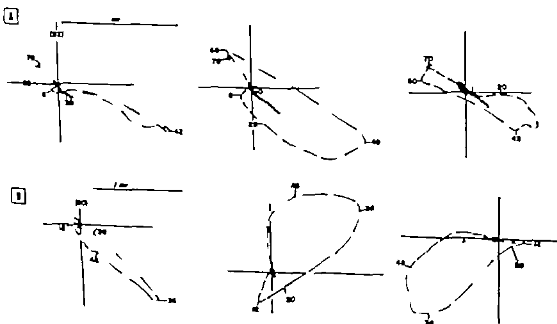


Fig 3 A Anterior dominance is demonstrated by the position R₁₀ (25 degrees). Two sharply defined S vectors are identified in fp and sp t 60 and 70 msec. The second, S causes brief complete reversal of transcription in hp. B Although the voltage is normal, the configuration, closely resembles that of volume overload of the left ventricle. R is sharply posterior Q is large relative t R, and the angle between R and S is unusually narrow

dle branch block.[26,27] The M_{hp} is at the S point but this feature is not commonly associated It is an independent unusual but apparently not abnormal variant

Fig 3 illustrates three sets with isolated criteria suggesting various entities. Clock wise initial rotation with a *horizontal* $loop_{fp}$ (B C) is ordinarily associated with inferior wall infarction[8,28] but the Q loop is narrow and not accompanied by prolonged initial superior duration[28] The dominantly anterior $loop_{hp}$ (A) brings to mind true posterior wall infarction but this *is a common variant and criteria for this* diagnosis are not clear-cut.[29] The counter clockwise rotation of the loop (C) has been attributed to anterior apical infarc tion[14,29] but is usual in patients without clinical disease who have left axis devia tion The ellipsoidal $loop_h$ (B) is similar to *those in patients with advanced LVH but* there are no supporting criteria.[31]

Fig 4 illustrates single examples of bizarre loops inadequately explained by the clinical data A has features suggesting infarction of the posterior wall[32] (no forces in the left posterior quadrant) or of right *incomplete bundle branch block or hyper* trophy (large rightward S vector) B also suggests right hypertrophy (anterior $loop_{hp}$) with clockwise rotation of the S segment

Fig 5 illustrates *still another* example of a dominantly anterior loop with a peculiar stall of transcription at 70 msec (A) The $loop_h$ (B) is reminiscent of vol ume overload of the left ventricle in the young because of the posterior R and a Q very large in relation to R[33] The voltages however were well *within* the *normal* range.

Conclusions

Seventy five clinically normal individ uals with a mean age of *51* were studied with the Helm sponge VCG and compared with a *similarly* selected group of 133 adults whose mean age was 24 years Unlike tracings recorded with the Frank VCG or standard ECG there was no decrease in spatial voltage in the older adults The latter have more *leftward* loops in the frontal plane and as a consequence higher voltage *in the* horizontal plane and lower ones in the sagittal. Loops from the older patients show less variability in voltage of Q vectors and of the position of the 20 msec. and maximum vectors. Females generally had shorter time measurements for the duration of QRS and the onset of the major vectors. They also had less posterior *voltage but there was no difference in* spatial voltages for the R or maximum vector as had been found in younger females. A table of normal values for five vectors is presented and the range further illustrated by nine examples of variants with some features suggesting disease *Clinically silent* scars cannot be excluded.

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Perfusion defects in the aging lung

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Scintiscanning of the lungs has become a standard procedure in the evaluation of patients with a variety of pulmonary diseases, particularly those patients thought to have acute pulmonary embolism [1-3] At the Coney Island Hospital where the patient population is older than in most hospitals we have been impressed with the frequency of abnormal scans that cannot be readily explained This impression prompted us to investigate the appearance of the lung scan in a group of elderly subjects.

Methods

The subjects chosen for this study were residents of the Chronic Disease Unit of the Coney Island Hospital which is composed principally of elderly patients in need of nursing and custodial care Eighty patients who were free of acute illness and clinical signs of cardiac decompensation received the following examinations (1) standard chest x ray with posteroanterior and lateral views (2) electrocardiogram (3) determination of serum glutamic oxalacetic transaminase lactic dehydrogenase and serum glutamic pyruvic transaminase levels (4) pulmonary function testing (maximum expiratory flow rate) (5) lung scan These procedures were repeated two months later in 59 patients

Lung scanning was performed after the intravenous injection of 300 μc of macroaggregated (10 to 70 μ) albumin [illegible] suspensions with the patient in the supine position Photoscanning was performed in black and white and direct print-out color records were produced by a commercial scanner with a 3 inch crystal and 19 hole collimator Scans were performed in both the prone and supine positions where possible The lungs were arbitrarily divided into upper middle and lower fields, and the number site and shape of all defects were recorded Abnormalities were classified as follows (1) patchy hypoperfusion (diffuse poorly defined areas of decreased blood flow) (2) peripheral focal defects (sharply defined areas of hypoperfusion in the periphery of the lung with a concave surface) (3) central defects related to en

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larged mediastinal structures such as heart and aorta (4) blunting of the costophrenic angle.

Chest films were carefully scrutinized for all abnormalities and in particular the following (1) changes of pulmonary fibrosis as manifested by an increase in interstitial markings and areas of focal hyperaeration (2) changes of chronic emphysema such as hyperaeration of the lungs flattening of the diaphragms, and increased diameter of the central pulmonary arteries w th abrupt diminution and narrowing of the peripheral branches (3) bullae as manifested by sharply demarcated areas devoid of bron chovascular markings (4) blunting of the costophrenic angles and pleural thickening (5) cardiomegaly and enlargement of the thoracic aorta.

The chest x rays and scans were first examined separately Following this initial survey each patient s scan and x ray were examined together in order to assess the correlation.

In 30 patients with scan abnormalities unexplained by x-ray a third lung scan was performed 3 to 7 months (mean of 5 months) after the initial examination In 19 patients, full-chest laminography with cuts 1 cm apart was performed on the same day

Results

The patients in this study remained stable with no clinical evidence of acute cardiopulmonary disease during the period of observation Serum enzymes remained normal and none developed electrocardiographic evidence of right ventricular strain or hypertrophy

Table I summarizes the findings of the initial survey Radiologic evidence of chronic lung disease was found in 24 and abnormal scans in 57 of the 80 patients.

Table I Summary of find ngs

Patients	*Mean ge*	*Mean MEFR in 35 patients (L./min.)*	*No. with -ray evidence of chronic lung disease*	*No. with abnormal scans*	*No. with unexplained scan abnormalities*
Male (28)	75 (62–96)	101 (42 220)	10	18	10
Female (52)	76 (60–92)	71 (12–95)	14	39	20
Total (80)	76 (60–96)	84 (12 220)	24	57	30

Table II Analysis f 30 patients with unexplained perfusion defects

Patients	*Mean ge*	*No. with peripheral focal defects*	*No. with patchy hypoperfusion*	*No. with hypoperfusion of at least 50 per cent of lung fields*
Male (10)	73 (62–91)	4	9	7
Female (20)	76 (60–84)	7	18	11
Total (30)	75 (60–91)	11	27	18

Fig 1 A marked dichotomy between chest roentgenogram and lung scan A The patient's chest x ray is normal except for a borderline heart size. B A lung scan shows patchy hypoperfusion of the right upper left middle nd left lower lung fields



Fig 2 An unexplained focal, peripheral defect. A Normal l ng fields on chest x-ray B A large peripheral scan defect with a concave medial border in the right middle lung field C A tomogram demonstrating vascular markings in the rea of the defect.

Of the 57 abnormal lung scans the defects corresponded to radiologic findings in 27 patients as follows lung disease alone (patchy hypoperfusion) 20 pleural disease alone (blunted costophrenic angles) 2 cardiac and aortic dilatation (central defects) 1 lung disease and cardiac enlargement (patchy hypoperfusion and central defects) 4 There was no correlation between scan defects and age in our series possibly because of a relatively small age spread Scans were abnormal in 68 per cent of patients over 75 years and in 78 per cent of those under 75

The 30 scans with unexplained defects are listed in Table II Although most of the defects consisted of patchy hypoperfusion

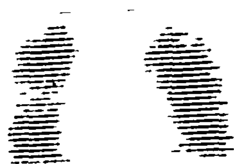


Fig 3 An unexplained peripheral defect is seen i the right middle lung field.

Fig 1) peripheral focal defects were found in 11 (Figs. 2 and 3) The abnormalities were unilateral in 22 and bilateral in 8 None of these abnormalities was changed on the repeat scans, but one patient developed a new focal defect in the course of the study

Tomograms were performed in 19 of the 30 patients with unexplained perfusion defects. They were normal in all but one patient whose films were consistent with chronic lung disease.

Maximum expiratory flow rates (MEFR) were uniformly low in 35 patients and could not be accurately determined in the others.

One patient with bilateral scan defects and a normal chest x-ray expired two months after the completion of this study At necropsy a patchy dilatation of alveoli was found throughout both lungs (Fig 4) The major pulmonary arteries and their branches were patent, and no histological evidence of microemboli was seen.



Fig 4 Lung scan of an autopsied patient. A The scan shows defect in the left upper lung field and patchy hypoperfusion of the right lower lung field. B A histologic section of the patient lungs shows generalized distension of alveoli (×5).

Discussion

Lung scintiscanning after the intravenous injection of radioiodinated macroaggregated albumin is a safe and useful method for evaluating the distribution of pulmonary blood flow The test depends on the temporary blockade of approximately one million of the 280 billion precapillary arterioles in the lungs by radioactive microemboli. Normally the distribution of radioactivity is relatively homogeneous with slightly less uptake in the apices than other areas especially if the macroaggregate is injected with the patient sitting The mediastinal structures including the heart and great vessels appear as sharply circumscribed areas of absent uptake.

It is apparent that a pulmonary artery embolus or thrombosis will prevent the labelled albumin from reaching the arterioles fed by the blocked artery resulting in an area of decreased or absent radioactivity However this perfusion defect is not specific for thromboembolic phenomena any condition that alters pulmonary blood flow will cause a similar or identical defect.[1-4] This includes granulomatous disease neoplasia, pneumonia, pulmonary fibrosis, obstructive emphysema and pleural effusions. Occasionally extreme cardiomegaly or a tortuous, dilated

Fig 1. A marked dichotomy between chest roentgenogram and lung scan. A. The patient's chest x-ray is normal except for a borderline heart size. B. A lung scan shows patchy hypoperfusion of the right upper, left middle and left lower lung field.

Of the 57 abnormal lung scans the defects corresponded to radiologic findings in 27 patients as follows: lung disease alone (patchy hypoperfusion) 20; pleural disease alone (blunted costophrenic angles) 2; cardiac and aortic dilatation (central defects) 1; lung disease and cardiac enlargement (patchy hypoperfusion and central defects) 4. There was no correlation between scan defects and age in our series possibly because of a relatively small age spread. Scans were abnormal in 68 per cent of patients over 75 years and in 78 per cent of those under 75.

The 30 scans with unexplained defects are listed in Table II. Although most of the defects consisted of patchy hypoperfusion



Fig 2. An unexplained focal peripheral defect. A. Normal lung fields on chest x-ray. B. A large peripheral scan defect with a concave medial border in the right middle lung field. C. A tomogram demonstrating vascular markings in the area of the defect.

elevations consistent with pulmonary embolization were found

The appearance of a defect on the lung scan is of some diagnostic importance. Poulose and associates[8] have noted that the well-delineated peripheral, concave defect is the usual finding in pulmonary embolism. This is thought to be the scan equivalent of the hemispherical lesions at the lung periphery seen at necropsy and the so-called Hampton HUMP seen on the chest roentgenogram. Although this finding was also seen in 36 per cent of patients with chronic obstructive pulmonary disease, the latter condition was generally associated with patchy diffuse hypoperfusion. In our series the scans of 27 patients exhibited the changes typical of chronic lung disease, but 11 had one or more peripheral concave defects. We cannot exclude the possibility that some of these latter abnormalities represented the residua of old organized emboli which would no longer show serial changes.

Finally the isolated scan abnormalities may be related to parenchymal changes in the lungs that occur with aging. Previous work has demonstrated the progressive development of interstitial fibrosis and distension of alveoli.[12] These findings are of little clinical significance and are not easily detectable with a chest x ray. When these changes are present, spotty areas of hypoperfusion might result from compression of small vessels by distended alveoli and physiologic shunting secondary to focal hypoventilation. The necropsy findings in one of our patients with a normal chest x ray and bilateral scan defects is consistent with this hypothesis.

Newer scanning techniques might be helpful in delineating further the etiology of isolated lung scan defects in the aged. For example, the uptake of radioactive xenon during normal respiration can be used as an index of regional ventilation.[13] In pulmonary embolism one finds normal ventilation in the area of hypoperfusion (as measured by uptake equilibration half times) whereas parenchymal lung disease results in decreased ventilation as shown by prolonged half times. Localized areas of bronchial obstruction have been detected with the use of an aerosol of macroaggregated albumin tagged with radioactive technetium.[14]

Although we cannot offer a definite etiology at this time it is clear that perfusion defects with and without chest x ray abnormalities are common in the aged. Consequently their lung scans must be evaluated with extreme caution. It is hazardous to allow the diagnosis of acute pulmonary embolism in an elderly patient to rest principally on this test. The scan should be used only as confirmatory evidence. When pulmonary embolism is suspected clinically the finding of a normal scan may help to rule it out, but an abnormal scan adds relatively little to the diagnostic probability. If the scan defects resolve or diminish in size in a characteristic fashion the diagnosis of pulmonary embolism can then be confirmed retrospectively.

Summary

A survey of 80 residents (mean age 75 years) of a geriatric chronic nursing unit revealed persistently abnormal lung scans in 57, 30 of whom had no roentgenographic evidence of pulmonary disease. None had any signs or symptoms of pulmonary embolism. Twenty-seven of the 30 scans with isolated perfusion abnormalities had areas of patchy hypoperfusion and 11 had one or more well-delineated defects. Full chest tomography was normal in 18 of 19 patients in this group of 30. Maximum expiratory flow rates were uniformly low.

Although a definite explanation for the abnormalities cannot be given, it is apparent that an abnormal lung scan in an elderly individual is of little or no predictive value in the diagnosis of acute pulmonary embolism.

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aorta may encroach sufficiently on the lungs to produce hypoperfusion Fortunately pulmonary disease whether acute or chronic usually produces an abnormal density on the chest roentgenogram whereas most pulmonary emboli (80 per cent) do not [4] Therefore the combination of a normal chest x ray and an abnormal scan has been taken as strong evidence for the diagnosis of pulmonary embolism

The patients in this study were representative of the geriatric nursing home population None was acutely ill at the time of scanning and yet the great majority (57 of 80 patients) had abnormal scans The prevalence of radiologic pulmonary abnormalities in our patients was higher than that previously reported for aged subjects [7] However most of the mild changes would ordinarily have been dismissed as insignificant had we not been looking specifically for an explanation for uneven pulmonary blood flow Furthermore one would expect to find evidence of chronic disease in a nursing home population more frequently than in the general population It is remarkable that 30 of the 80 patients (38 per cent) had the constellation of roentgenographically normal lungs and an abnormal scan despite this narrow definition of normality for the chest film It is most unlikely that the perfusion defects were artifactual because they were reproducible in each case

The explanation for abnormal pulmonary blood flow distribution in the absence of obvious pulmonary disease is not clear It is possible that chronic lung disease undetectable by chest roentgenogram contributed to the high prevalence of scan abnormalities. Obstructive emphysema and resultant cystic changes are notoriously difficult to recognize on the standard chest film Poulose, Reba and Wagner[8] reported that only 40 per cent of their patients with obstructive pulmonary disease and abnormal scans had abnormal chest films. In the search for x ray abnormalities we obtained full chest laminograms in 19 of the 30 patients but found an abnormality in only one patient. However we cannot rule out the possibility that generalized or regional obstructive bronchial disease contributed to the abnormal perfusion

Second functional changes within the lungs might be responsible for perfusion defects It is well known that pulmonary function decreases with age and this is reflected in a lower partial pressure of oxygen in arterial blood [9] Therefore, the finding of low maximum expiratory flow rates in our patients was not unexpected. Although this test is primarily used for the detection of bronchial obstruction the result is also dependent on the state of the chest wall and the efficiency of the skeletal muscle that enables it to expand and contract forcefully Since our patients were not only elderly but also debilitated it is likely that their respiratory effort was impaired possibly accounting for the low mean MEFR Regardless of its etiology it is reasonable to suspect that a decrease in total lung function might be associated with uneven ventilation Physiologic shunting of blood flow away from the areas with relatively less ventilation could then account for regional hypoperfusion as seen on the lung scan [4]

A third possible explanation is that some of the defects represent thromboemboli. Microscopic pulmonary thromboembolism is a common necropsy finding in patients over the age of 60 [10] The etiology of these arterial lesions is not certain but they may be the result of repeated small emboli from the veins of the lower extremities and pelvis. Our patients were not only elderly but also sedentary and might have been prone to develop emboli It is very unlikely however that these defects represented acute or recent pulmonary embolism because they remained unchanged in appearance on serial scans over many months. Tow and Wagner[11] have shown that a changing scan pattern is characteristic of emboli in contradistinction to chronic lung disease The defects caused by small pulmonary emboli generally show some signs of at least partial resolution within a month Furthermore 70 per cent of the group with abnormal scans and normal x rays had hypoperfusion of at least half of the lung fields Such extensive involvement from acute pulmonary embolism would be expected to produce signs of severe clinical illness. Yet none of the patients developed dyspnea hemoptysis, or pleuritic chest pain and no electrocardiographic changes or serum enzyme

elevations consistent with pulmonary embolization were found

The appearance of a defect on the lung scan is of some diagnostic importance. Poulose and associates[4] have noted that the well-delineated peripheral concave defect is the usual finding in pulmonary embolism. This is thought to be the scan equivalent of the hemispherical lesions at the lung periphery seen at necropsy and the so-called 'Hampton HUMP' seen on the chest roentgenogram. Although this finding was also seen in 36 per cent of patients with chronic obstructive pulmonary disease the latter condition was generally associated with patchy diffuse hypoperfusion In our series, the scans of 27 patients exhibited the changes typical of chronic lung disease, but 11 had one or more peripheral concave defects. We cannot exclude the possibility that some of these latter abnormalities represented the residua of old, organized emboli which would no longer show serial changes.

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Electrocardiographic changes in infants undergoing surface-induced deep hypothermia for open heart surgery

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The relatively high mortality rate associated with certain palliative procedures and with cardiopulmonary bypass in infants has stimulated the development of a method of surface-induced hypothermia for open-heart surgery at this institution. Patients with severe congenital heart lesions amenable to total correction within a limited time period and who were deteriorating despite vigorous medical management have been selected for surgical repair under hypothermia.[3] Details of this procedure have been previously reported; basically it involves the use of deep-ether anesthesia, respiratory alkalosis, and low molecular weight dextran.

The fear of ventricular fibrillation has been a deterrent to widespread acceptance of surface cooling. However, using this technique ventricular fibrillation has not occurred throughout the entire procedure in our experience with 26 patients, except during resuscitation of a few infants who had an uncorrectable lesion or one corrected improperly. This study was undertaken to document the relative stability of cardiac action under deep hypothermia and to provide information on the seemingly well tolerated and reversible changes in the electrocardiogram (ECG) which do occur in the infant subjected to cooling.

Methods and materials

The ECGs recorded during cooling and rewarming in each of 14 patients were technically suitable and complete enough for detailed evaluation. The ages of the patients ranged from 78 hours to 16½

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months with a mean of 3 9 months There were 12 males and 2 females with an average body weight of 4 2 kilograms (range 2 7 to 6 1 kilograms) Despite the complex nature of the cardiac malformations complete correction rather than palliative surgery was attempted in each patient (Table I)

Hypothermia was achieved by placing the anesthetized infant in a tank of ice. Body temperature was determined from a thermal probe placed high in the rectum and was believed to closely approximate myocardial temperature Although ice bags were placed over the anterior surface of the patient the precordial area was left exposed thus avoiding direct cooling of the heart.

Table I *Major congenital heart defects in the 14 infants undergoing surface-induced deep hypothermia for total surgical correction**

Congenital heart defect	*No of patients*
Total anomalous pulmonary venous drainage	6
Transposition of the great vessels	3
Pulmonary atresia with atrial septal defect and patent ductus arteriosus	2
Ventricular septal defect and double-outlet right ventricle	1
Ventricular septal defect and atrial septal defect	1
Tetralogy of Fallot†	1
Total	14

*ECG' in another 12 infants undergoing hypothermia were not complete enough for detailed analysis.

†Preoperative diagnosis of this case was ventricular septal defect.

Standard limb Lead II was routinely used for continuous monitoring however in several cases Lead I or III was utilized because of less electrical interference. A recording was made at every few degrees centigrade change during cooling and rewarming Analysis of these tracings included notation of rate and rhythm and measurement of the P R QRS and Q-T intervals. The distribution mean and standard deviation of intervals were plotted for several temperatures. The normal Q-T interval for slow heart rates at normothermia was obtained from tables of standard values[5] and compared to those measured at the same heart rate under hypothermia

The Q-T/R R was determined using the Q-T interval in hypothermia and the standard Q-T interval for the same heart rate at normothermia. Since the Q-T interval represents mechanical systole,[6,7] the Q-T/R R is the fraction of the cardiac cycle which is occupied by mechanical systole

The amplitude of the Q R and S waves was measured in all tracings. A careful search was made for the appearance of unusual waves and changes of configuration of the P QRS and T complexes.

Results

The typical electrocardiographic changes observed during cooling are illustrated by the tracing taken on a 4-month-old male infant undergoing hypothermia for correction of total anomalous pulmonary venous drainage (Fig 1) All patients had a progressive decline in heart rate with prolongation of the P R QRS and Q-T intervals as body temperature was lowered (Table II)

Table II *Mean and standard deviation of heart rate P R QRS and Q T intervals during cooling of 14 infants*

Temperature (° C.)	*Heart rate*	*P R (sec)*	*QRS (sec)*	*Q-T (sec.)*
37	176 0 ± 29 18	0 112 ± 0 023	0 058 ± 0 019	0 220 ± 0 025
30	110 7 ± 13 45	0 147 ± 0 017	0 070 ± 0 018	0 311 ± 0 026
25	67 0 ± 11 23	0 182 ± 0 024	0 105 ± 0 021	0 480 ± 0 077
20	42 4 ± 10 39	0 226 ± 0 034	0 121 ± 0 028	0 655 ± 0 098

Fig. 1. Standard Lead II ECG of a 4-month-old male infant undergoing hypothermia for correction of total anomalous pulmonary venous drainage. Paper speed 25 mm. per second.

Cooling

RHYTHM. Normal sinus rhythm without extrasystoles was maintained to 21° C. in all patients. Below this temperature surgical manipulation of the heart was begun and nodal rhythm or ventricular extrasystoles often developed. A return to sinus rhythm occurred in some cases when manipulation ceased. This was documented at 18° C. in two cases and at 17° C. in one. Although ventricular extrasystoles were seen during cardiac manipulation, ventricular fibrillation did not occur.

RATE. The heart rate declined rapidly during the initial phases of cooling, but the rate of decline was less at a lower body temperature (Fig. 2). The mean heart rate changed from 176 at 37° C. to 42.4 at 20° C. Thus at 20° C. the mean heart rate was 24 per cent of that at normothermia.

P-R INTERVAL. A progressive increase in the P-R interval was seen during cooling (Fig. 3). From a mean value of 0.112 sec. at 37° C., it prolonged to 0.226 sec. at 20° C. Those patients who were still in sinus rhythm below 20° C. had P-R intervals of

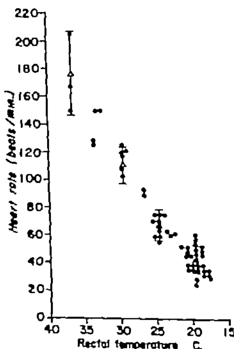


Fig. 2. Distribution of heart rate of patients undergoing surface-induced deep hypothermia. Mean (Δ) and standard deviation (I) have been calculated for 37, 30, 25 and 20° C.

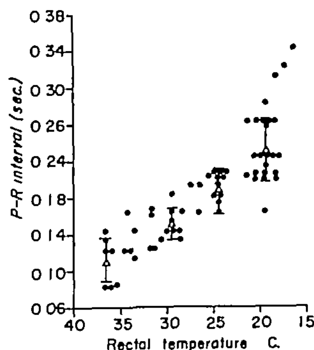


Fig 3 Distribution of P-R interval of patients undergoing surface-induced deep hypothermia. Mean (Δ) and standard deviation (Ī) have been calculated for 37 30 25 and 20° C

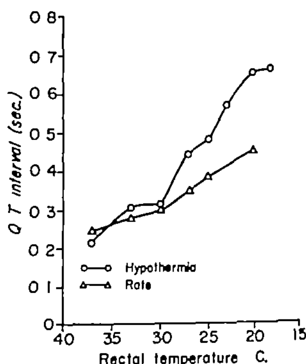


Fig 5 Comparison of the Q-T interval observed under hypothermia and Q-T for the same heart rate at normothermia.

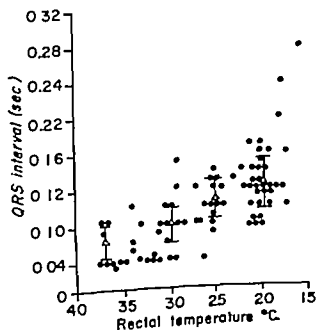


Fig 4 Distribution of QRS interval of patients undergoing surface-induced deep hypothermia. Mean (Δ) and standard deviation (Ī) have been calculated for 37 30, 25 and 20° C.

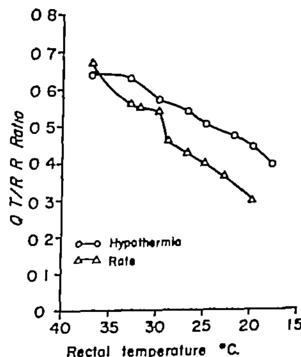


Fig 6 Comparison of the Q-T/R-R observed under hypothermia and Q-T/R R for the same heart rate at normothermia.

0.24 and 0.32 sec. at 18° C and 0.34 sec. at 17° C

QRS INTERVAL. The distribution of the QRS interval in all patients is illustrated in Fig 4 A progressive widening of the QRS occurred as body temperature was lowered. The mean increased from 0 058 sec. at 37° C to 0 121 sec. at 20° C Below 20° C. the QRS intervals usually extended to 0 12 sec. or greater except in patients with sinus rhythm who demonstrated a QRS interval of 0.10 sec. to 0 12 sec. at 18 to 17° C

Q-T INTERVAL. The Q-T interval increased progressively from a mean of 0.22 sec. at 37° C to 0 65 sec. at 20° C. Changes of the Q-T intervals during hypothermia and of a correspondingly slow heart rate at normothermia are demonstrated in Fig 5 Prolongation of the Q-T interval during hypothermia was greater than would be expected from decreasing heart rate alone.

The mean Q-T/R R declined from 0 64 at 37° C. to 0.39 at 18° C For the same heart rates at normothermia one would expect a decline from 0 67 to 0.295 (Fig 6) For any given heart rate the ratio is higher in hypothermia than the same rate at normothermia which reflects greater prolongation of the Q-T under hypothermia.

WAVE CONFIGURATION As body temperature was lowered the amplitude of the P wave decreased in several patients but was unchanged in others. In no case did it increase or become notched or inverted. The great majority of patients had no significant change in the QRS voltage during cooling from 37 to 20° C., but in three cases a slight increase occurred and in one the voltage decreased. The T waves remained upright throughout in all but two patients. T wave inversion occurred at 31 C in one and at 18° C. in the other Minor S-T-segment shifts occurred in several patients, but no predictable pattern was observed Abnormal waves or bizarre

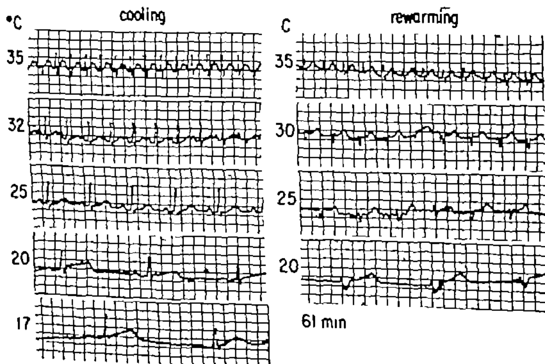


Fig 7 ECG changes in 1-month-old male infant (5.5 kilograms) undergoing hypothermia for total correction of transposition of the great vessels. Cardiac arrest time was 50 minutes, and 61 minutes elapsed from the beginning of arrest until the 20° C. rewarming These tracings are standard Lead II taken at paper speed of 25 mm. per second.

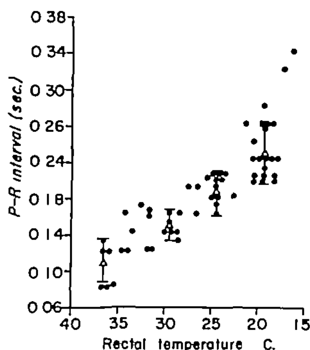


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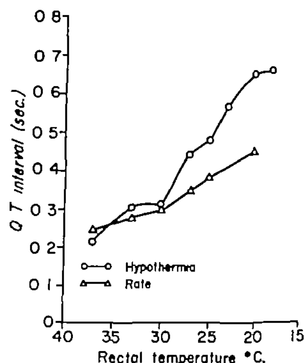


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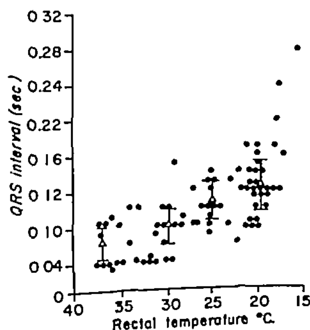


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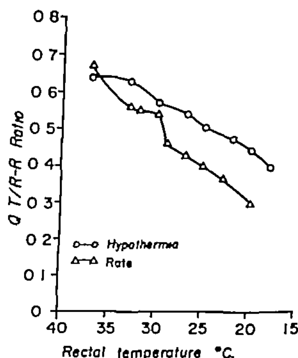


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QRS INTERVAL. The distribution of the QRS interval in all patients is illustrated in Fig. 4. A progressive widening of the QRS occurred as body temperature was lowered. The mean increased from 0.058 sec. at 37° C. to 0.121 sec. at 20° C. Below 20° C. the QRS intervals usually extended to 0.12 sec. or greater except in patients with sinus rhythm who demonstrated a QRS interval of 0.10 sec. to 0.12 sec. at 18 to 17° C.

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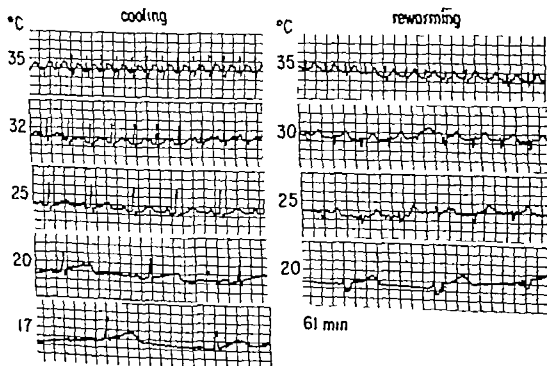


Fig. 7. ECG changes in 3-month-old male infant (5.5 kilograms) undergoing hypothermia for total correction of transposition of the great vessels. Cardiac arrest time was 50 minutes, and 61 minutes elapsed from the beginning of arrest until the 20° C. rewarming. These tracings are standard Lead II taken at paper speed of 25 mm. per second.

configurations of the P QRS or T waves did not develop

Rewarming The mean period of total circulatory arrest in these 14 patients was 44 minutes (range 25 to 64) Upon resuscitation the initial electrocardiogram was difficult to interpret because of the necessity of cardiac massage and mechanical or electrical pacing for varying periods Vasopressors calcium chloride and cardiotonic agents were also utilized on occasion Heart rate progressively increased during warming with the same general pattern as observed during cooling Although the QRS was extremely wide at first it gradually shortened and returned toward normal with time Many patients reverted to sinus rhythm between 30 and 34 C (Fig 7) Nodal rhythm persisted for 10 days in one patient with transposition of the great vessels and for 1 to 20 days in three patients with total anomalous pulmonary venous drainage One patient with anomalous pulmonary venous return was still in nodal rhythm when seen last (5 months postoperatively)

Discussion

Interpretation of results obtained during hypothermia must be made with careful consideration of the specific method used since factors such as anesthetic agents ventilation acid base balance and electrolyte status can markedly alter the variables under consideration Age and species are also important factors in reaction to cold younger subjects are most tolerant of low body temperature [8]

Hypothermia consistently causes a slowing of the metabolic processes in cardiac tissue resulting in depression of higher centers of rhythmicity and slowing of conduction Heart rate progressively declines and there is prolongation of the P R QRS and Q-T intervals.[8, 12] Ventricular fibrillation has been a serious complication with many previous methods of hypothermia [13] However the precise factors which render the heart vulnerable to this arrhythmia are unknown A frequent observation by others has been instability of rhythm during cooling (of adults and children) with the spontaneous development of atrial fibrillation wandering atrial pacemaker or nodal rhythm between 34 and 25° C [1, 12, 14]

In our patients arrhythmias were not observed above 21 C or before surgical manipulation This may be related to the specific method or to the fact that all of our patients were infants. It has been shown that during hypothermia arrhythmias occur less frequently in children than adults.[11, 13]

The amplitude of the Q R and S waves have been reported to both increase[13] and decrease[11] during hypothermia but these changes could not be related to any definite temperature or other specific factor Although the development of Q waves and notched R waves has been described [11] none of the infants in this series had such changes in the leads recorded

Alterations in the S-T segment and T wave of dogs cooled under ether or sodium barbital anesthesia have been reported by Hook and Starmont [15] As body temperature approached 20° C the T waves became diphasic, then deeply and bizarrely inverted but returned to normal upon rewarming The observations in our clinical series as well as others[11, 12] suggest that the ST T changes in humans do not follow any specific pattern Elevation depression or no change in the S-T segment have all been observed T wave inversion occurred in only 2 of our 14 patients and the remainder developed no abnormalities of the T waves.

The appearance of abnormal waves in the ECG during hypothermia has been observed by several investigators,[14, 16, 17] however their significance is yet to be elucidated Osborn[16] described a positive deflection very closely following the QRS complex and appearing in the great majority of animals later developing ventricular fibrillation He ascribed this pattern to a current of injury These animals were initially allowed to breathe spontaneously[8] then at approximately 25° C when hypoxia and acidosis developed they were ventilated In animals continuously ventilated from the onset the wave did not appear suggesting that its occurrence may have been due to inadequate elimination of CO_2 rather than low temperature Other investigators were unable to abolish these waves by hyperventilation but only moderate degrees of alkalosis were attained [14]

The fact that abnormal waves did not

appear in the tracings of any of our patients may be related to the method itself or to the patient's age. However, these infants were monitored with only a single limb lead and this may not be adequate to detect the appearance of these waves. This point has been emphasized by Emslie-Smith and associates who demonstrated the existence of such waves in all of their patients and experimental animals by using multiple leads. Reportedly, the wave was present in the epicardial or precordial lead even when it was absent in the limb leads.

Although there is a prolongation of the Q-T interval, the Q-T/R-R declines during cooling. Since the Q-T interval corresponds to mechanical systole, it can be seen that the systolic period occupies relatively less of the total cardiac cycle with decreasing temperature. Berne[1] has demonstrated this experimentally and found that at normothermia mechanical systole was 47 per cent of the cardiac cycle but this declined to 22 per cent at 20.5° C. In animal studies utilizing normal ventilation and normal pH, Mohri[9] found that the Q-T/R-R, with spontaneous cardiac action, decreased to 30 to 35 per cent around 18° C, when ventricular fibrillation sometimes occurred. However, by shortening the diastolic phase with electrical pacemaking, ventricular fibrillation could be avoided and effective cardiac output maintained even to 10° C. It was observed that with pacing the Q-T/R-R increased to 60 per cent at 20° C and 40 per cent at 10° C.

In the present clinical series the Q-T/R-R observed under hypothermia remained quite high despite the absence of pacing. At 20° C, the Q-T interval occupied 44 per cent of the cardiac cycle and at 18° C it was still 39 per cent. This may be one of the reasons for the absence of ventricular fibrillation in our patients.

Many trials to eliminate the incidence of ventricular fibrillation during hypothermia have been carried out despite the absence of knowledge concerning its pathophysiology. There is lack of agreement on the best method of preventing fibrillation and different investigators have obtained contradictory results using the same agent. Alteration of acid-base balance[29-31] and electrolytes[31-33] have been attempted with variable results. Numerous pharmacological agents,[11, 13, 34-36] including quinidine, procainamide, digitalis, Prostigmine, and acetylcholine, and surgical procedures,[37] such as bilateral sympathetic denervation and bilateral cervical vagotomy have also been investigated. However, none of these techniques were effective in completely eliminating ventricular fibrillation and are not now being used clinically.

Our method of surface-induced deep hypothermia has not been associated with the occurrence of ventricular fibrillation during cooling to 14 to 19° C. The relative importance of each factor in preventing fibrillation is not clear at this time; however, deep levels of anesthesia with ether and respiratory alkalosis (pH 7.8 to 7.9) are felt to be important. This method has been applied with total circulatory arrest for up to 90 minutes without ventricular fibrillation during cooling and without death in over 300 dogs.

Summary

Serial electrocardiographic tracings of 14 infants undergoing surface-induced deep hypothermia for total correction of various congenital heart lesions have been reviewed. As body temperatures declined to 18° C, there was a progressive decrease in heart rate and prolongation of the P-R, QRS, and Q-T intervals. All patients remained in normal sinus rhythm until surgical manipulation of the heart was begun at around 18 to 20° C, whereupon most went into nodal rhythm with occasional ventricular premature contractions. None of these cases developed ventricular fibrillation during cooling. However, at resuscitation, ventricular fibrillation occurred in a few infants where proper correction of the cardiac lesion had not been accomplished. There was no consistent change in the S-T segment or T wave, and abnormal waves did not appear. During rewarming the heart rate increased progressively, the QRS became narrower, and many patients reverted to sinus rhythm at 30 to 34° C. These results demonstrate that this method of deep hypothermia can eliminate ventricular fibrillation in infants.

The authors wish to express their appreciation to Dr. Warren G. Guntheroth for his helpful review of this manuscript.

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Femoral artery occlusion following percutaneous catheterization

Frank E. Kloster, M.D.
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Femoral artery thrombosis is the most frequent complication of retrograde aortic catheterization by the percutaneous technique.[1-4] With proper treatment it usually causes no residual disability but is a distinct source of morbidity in terms of patient discomfort, the risk of loss of the limb, the need for an operative procedure, and extended hospitalization. Experience at the University of Oregon Medical School suggested that certain patients are more likely to develop femoral artery thrombosis. Since 1964 we have kept careful prospective records on all patients undergoing cardiac catheterizations, initially as participants in the Cooperative Study on Cardiac Catheterization. We have reviewed these records to attempt to identify factors which may predispose to arterial occlusion following percutaneous catheterization.

Methods

Technique. Retrograde arterial studies are performed percutaneously through the right femoral artery using the Seldinger technique.[5,6] The skin is surgically prepared and the tissue around the artery is infiltrated with 1 per cent lidocaine as local anesthetic. The femoral artery is punctured with an 18 gauge thin-walled Cournand needle which passes through the artery and out the posterior wall. The needle is slowly withdrawn until the arterial lumen is entered and a good pulsatile blood flow occurs. A 0.035 inch spring guide wire† is inserted, the needle is removed, and a no. 6 or 7 French (Fr.) Teflon Gensini catheter‡ is inserted over the guide wire and advanced to the heart. Recently a no. 8 Fr. Ducor pigtail catheter§ and a 0.038 inch Teflon-coated guidewire have been used occasionally. The catheter is aspirated vigorously whenever it has contained a guidewire or blood and is flushed at frequent intervals with normal saline solution containing heparin (2,000 units per 500 ml.). The catheter typically remains in the artery for 60 to 90 minutes. When it is removed at the end of the pro-

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§Cordis Corporation, Miami, Fla.

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Femoral artery occlusion following percutaneous catheterization

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Femoral artery thrombosis is the most frequent complication of retrograde aortic catheterization by the percutaneous technique.[1-4] With proper treatment it usually causes no residual disability, but is a distinct source of morbidity in terms of patient discomfort, the risk of loss of the limb, the need for an operative procedure, and extended hospitalization. Experience at the University of Oregon Medical School suggested that certain patients are more likely to develop femoral artery thrombosis. Since 1964, we have kept careful prospective records on all patients undergoing cardiac catheterizations, initially as participants in the Cooperative Study on Cardiac Catheterization. We have reviewed these records to attempt to identify factors which may predispose to arterial occlusion following percutaneous catheterization.

Methods

Technique. Retrograde arterial studies are performed percutaneously through the right femoral artery using the Seldinger technique. The skin is surgically prepared and the tissue around the artery is infiltrated with 1 per cent lidocaine as local anesthetic. The femoral artery is punctured with an 18 gauge thin walled Cournand needle which passes through the artery and out the posterior wall. The needle is slowly withdrawn until the arterial lumen is entered and a good pulsatile blood flow occurs. A 0.035 inch spring guide wire† is inserted, the needle is removed, and a no. 6 or 7 French (Fr.) Teflon Gensini catheter‡ is inserted over the guide wire and advanced to the heart. Recently a no. 8 Fr. Ducor pigtail catheter§ and a 0.038 inch Teflon-coated guidewire have been used occasionally. The catheter is aspirated vigorously whenever it has contained a guidewire or blood and is flushed at frequent intervals with normal saline solution containing heparin (2,000 units per 500 ml.). The catheter typically remains in the artery for 60 to 90 minutes. When it is removed at the end of the pro-

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‡United States Catheter and Instrument Corp., Glens Falls, N.Y.
§Cordis Corporation, Miami, Fla.

Table I Percutaneous femoral artery catheterisations July 1964 through April 1969

Total number of tudies	533
Femoral artery occlusions	7
Incidence	1 3%
Predominant mitral stenosis	113
Femoral artery occlusions	5
Incidence	4 4 %

cedure firm pressure is applied over the puncture site for 10 minutes at which time all bleeding has usually stopped if not pressure is reapplied until there is no fur ther bleeding An elastic pressure dressing is applied and left in place overnight

The patient is routinely examined for signs of arterial occlusion or other compli cations immediately after returning to his bed one hour later in the evening and the following morning before leaving the hospital Most are seen again within 2 to 6 weeks in the Outpatient Clinic With such repeated observations it seems probable that virtually all complications are de tected

Results

Incidence In the Cardiac Catheteriza tion Laboratory from July 1964 through April 1969 533 patients underwent per cutaneous retrograde femoral artery cathe terization Seven patients developed fem oral artery occlusion after catheterization during this 5 year period an overall inci dence of 1 3 per cent (Table I) Of the total group 113 patients had predominant mitral stenosis. Five of these developed femoral artery occlusion after retrograde femoral arterial studies an incidence of 4 4 per cent. The incidence in the remain ing 420 patients who did not have mitral stenosis was 0 48 per cent.

Clinical findings Pertinent data con cerning the patients who developed femoral artery occlusion are shown in Table II All were women between the ages of 31 and 54 years As indicated above 5 had pre- dominant mitral stenosis 2 with associated aortic or tricuspid valve disease One of the remaining patients had moderate aortic insufficiency and the other had a myo- cardiopathy of undetermined cause

Some difficulty was encountered entering the femoral artery with the needle in 3 patients (C A J T and K S) a frequent experience in patients with mitral stenosis and diminished peripheral pulses. Six pa tients had no 7 Fr Gensini catheters in- serted initially and no 8 Fr pigtail catheters were used subsequently in 2 Patient K S inadvertently had a no 8.5 Fr Brockenbrough Teflon catheter* in serted The catheter was removed after being advanced to the aortic bifurcation pressure was applied over the artery until bleeding stopped and a new puncture was made for insertion of a smaller Gensini catheter Patient E M had unusual trauma at the femoral artery puncture site because difficulty was encountered in pass- ing the aortic bifurcation and a tortuous aortic arch necessitating considerable cath- eter manipulation and replacement with a pigtail catheter All other studies were technically unremarkable

Five patients developed symptoms and findings of arterial occlusion while in the Cardiovascular Laboratory and a sixth had a cold painful pulseless foot soon after returning to the ward Patient O B had no symptoms or reported findings of ischemia in her lower extremities while in the hospital but developed intermittent claudication 3 days after the procedure and was found to have absence of pulsa tions in her right femoral artery and lower extremity

Operative findings Five patients under went surgical exploration of the obstructed artery within 12 hours of cardiac cathe- terization In each instance the femoral artery was exposed in the region of the puncture site an arteriotomy was made over the puncture the vessel lining was inspected and Fogarty catheters† were passed above and below for removal of obstructing material [7] The exploration was carried out over the left iliac artery in Patient K S because of symptoms on that side Patient D M had a cool pale pulse- less, mildly painful right lower extremity initially but gradually developed improved pulsations and skin color and was free of

*United States Catheter and Instrument Corp Glen Falls, N Y

†American Hospital Supply C Redmond, Wash.

Table II Patient data

Patient	Age (yr.)	Sex	Diagnosis	Catheter size (Fr.)	Time in artery (min.)	Cardiac index (L./min./M.²)	Mean LA pressure (mm. Hg)	Systemic pressure (mm. Hg)	Operative findings
E. H	48	F	MS, TS	7	90	2.3	14	120/70 (90)	Small vessels, thrombus
J. T	31	F	MS	7	30	2.5	24	105/75 (85)	Small vessels, atheroma, thrombus
C. A.	41	F	MS	7	60	2.8	18	135/65 (90)	Small vessels, embolus
K. S.	63	F	MS, AS	8.5	40	2.1	27	110/46 (70)	Small vessels, embolus
D. M.	43	F	MS	8	20	—	14	135/65 (95)	Not operated upon
O. B.	54	F	Myocard.	7	60	3.0	4	180/75 (100)	Small vessels, atheroma, thrombus
E. M.	45	F	AI	8	45	3.1	9	165/65 (95)	Intimal flap

Abbreviations: LA, Left atrial; MS, mitral stenosis; TS, tricuspid stenosis; AS, aortic stenosis; Myocard., myocardiopathy; AI, aortic insufficiency.

resting pain or claudication by the second day after catheterization. Subsequently plethysmography demonstrated adequate pulsations in the right lower extremity although pulses in the dorsalis pedis and posterior tibial vessels remained diminished as compared to the left. Patient O. B. returned to the hospital 4 weeks after catheterization after being followed by her local physician for continuing numbness and claudication in the right lower extremity associated with absent pulsations below the femoral artery. She underwent translumbar angiography which demonstrated an occluded right external iliac artery and underwent an arterial exploration the following day as described above.

The operative findings are listed briefly in Table II. It is of particular interest that unusually small iliofemoral arteries were observed in 5 of the 6 patients who underwent arteriotomy. In only one instance, Patient E. M., was there an intimal flap or evidence of local vascular trauma as cause of obstruction. In all others the site of arterial puncture was apparent only as a small red spot on the adventitial and intimal surfaces with no distortion of the vessel and with minimal or no hemorrhage around the vessel. Two patients with mitral stenosis were found to have pre-existing organized emboli which appeared to have been dislodged by the catheter and re-oriented in the vessel in an obstructing position. In Patient K. S. the embolic material was apparently displaced from the aortic bifurcation and passed into the left iliac system. Two others with mitral stenosis had fresh thrombus material occluding the vessels proximal to the arterial puncture site. In one, a 31 year-old woman, this was related to an atheroma which obstructed approximately 50 per cent of the arterial lumen. The final patient, O. B., was found to have several atheromatous lesions in her iliofemoral system and distal aorta and organizing thrombus overlying an intimal plaque proximal to the site of arterial puncture.

The 5 patients who underwent early arterial exploration have all had good functional results with return of normal pulsations in the affected extremity and all are free of symptoms of ischemia. Patient D. M., who was not operated upon, continues to have diminished pulsations in the affected extremity but does not have claudication. Patient O. B. continued to have diminished pulsations in the right lower extremity and claudication pain following late removal of intimal plaques and organizing thrombus material. Two years later she had further arteriography which demonstrated a small aortoiliac system with diffuse atherosclerotic disease and a persistent occlusion of the right iliofemoral arteries. She underwent a by-pass procedure with a Teflon graft but continues to have claudication in that extremity.

Hemodynamic findings. Because of the increased incidence of femoral artery occlusion in patients with mitral stenosis it was suspected that hemodynamic abnormalities related to this entity might be contributory to arterial complications.

Hemodynamic findings in patients who developed arterial occlusions are included in Table II The cardiac index was abnormally low in 2 patients with mitral stenosis and borderline in 2 others. Flow was normal in the 2 patients without mitral valve disease The pulmonary wedge pressure was normal in the latter 2 patients but was elevated in all with mitral stenosis. Systemic arterial pressure was somewhat low in 2 patients with mitral disease

Discussion

The reported incidence of femoral artery occlusion following percutaneous retrograde catheterization varies widely from near zero to over 7 per cent.[1-4, 8, 10] The incidence in this series is very similar to the 1 1 per cent occurrence in 1 460 procedures in the Cooperative Study on Cardiac Catheterization[1] and the 1 6 per cent incidence in 1 000 cases reported by Haut and Amplatz[10] Kottke and associates[4] and Mortensen[3] have concluded that reports of very low complication rates probably reflect incomplete follow up observations

Femoral artery occlusion occurred over three times more frequently in patients with predominant mitral stenosis than in the total patient population and ten times more commonly than in those without mitral stenosis. Beckman[11] and Lang[3] have also observed an increased incidence of femoral thrombosis in individuals with mitral valve disease. Further investigation including operative findings provides some insight into the reasons for the higher incidence of arterial complications in these patients.

Pre-existing local mechanical factors were present in most of our patients who developed femoral occlusion Most striking was the frequent occurrence of unusually small iliofemoral arteries. When examined surgically and angiographically in one instance they were found to be significantly smaller than the usual femoral and iliac vessels by numerous observers. While arterial spasm might have accentuated this appearance the observations were made by vascular surgeons with extensive experience in evaluating such vessels. These findings correlate well with clinical observations that individuals with mitral stenosis frequently have small arterial pulses and that arterial puncture is often difficult in such patients. In addition 2 individuals had atheromatous lesions near the catheter entry site which further compromised the arterial lumen In both of these occlusion was due to thrombus material superimposed on previous atheromatous narrowing In all patients with diminished arterial lumen size it seems likely that introduction of the catheter compromised the arterial lumen sufficiently to obstruct flow and permit platelet aggregation and the subsequent chain of events leading to intra arterial clotting

Two patients with mitral stenosis had obstruction due to organized emboli which clearly antedated the cardiac catheterization The left atrium was entered in neither In one the onset of symptoms of ischemia in the leg opposite that being catheterized was closely related to passage of the catheter past the aortic bifurcation In both the catheter apparently dislodged a previously nonobstructing arterial embolus, allowing downstream migration and arterial obstruction

Despite frequent concern about the risk of elevating a flap of intima with the catheter and producing arterial obstruction this complication occurred only once in this series. In this patient unusual trauma occurred as a result of difficulty in manipulation of the catheter At the time of the operation a piece of intima and several bits of thrombotic material were removed with the balloon catheter In all others the site of arterial puncture appeared quite benign with only a tiny red spot on the adventitial and intimal surfaces to indicate where the puncture had been made a few hours previously There was significant hematoma around the artery in none

A borderline or low cardiac output was found in the 4 patients with mitral disease in this series in whom it was measured This has also been observed with increased frequency in patients developing arterial occlusion in other studies.[8,11] If arterial flow is already diminished because of low output this may be an additional factor predisposing to stasis and clotting when a catheter is introduced into the vessel The

high incidence in women is striking and was also recognized by Haut and Amplatz.[6] Whether there is a causal relationship possibly a greater occurrence of small arteries in women or if this is simply related to the higher incidence of mitral stenosis in females is unclear

Certain precautions seem indicated when performing percutaneous femoral artery studies in patients who appear predisposed to arterial occlusion. This group includes individuals with mitral valve disease particularly stenosis, those with weak peripheral arterial pulses or with clinical evidence of low cardiac output, and patients with a history or physical findings of pre-existing arterial occlusive disease either atherosclerotic or embolic. The catheter should be of the smallest size consistent with a satisfactory study and the procedure should be planned to minimize the time the catheter is in the artery Extensive manipulation or repeated catheter changes which might traumatize the vessel should be avoided. Excessive pressure should not be exerted to control bleeding when the catheter is removed.[5-11] Finally the increased risk of thrombosis should be recognized and the patient should be observed especially closely in the postoperative period.

Six of our 7 patients developed evidence of arterial occlusion by the end of the catheterization or shortly thereafter This is consistent with Ross conclusion that the presence of a normal arterial pulse at the end of the procedure makes thrombosis unlikely Conversely a cold pale pulseless painful extremity strongly suggests arterial occlusion and the probable need for thrombectomy Persistent signs of ischemia during a 4 to 6 hour period of observation is an indication for arterial exploration There may be some degree of clinical improvement during this time probably due to decreasing vasospasm but complete clearing of evidence of ischemia has not been common. Continued discrepancies between the two lower extremities in skin temperature and color arterial pulses, and capillary filling times or continued discomfort have consistently been associated with vascular occlusion in our experience. Early arteriotomy and thrombectomy using the catheter technique have been simple and benign procedures. These have resulted in prompt restoration of arterial patency with no residual symptoms of vascular insufficiency in this group and in a previously reported study.[11] When thrombectomy was not carried out promptly despite persistent evidence of ischemia, claudication commonly resulted

Summary

Femoral artery occlusion occurred in 7 of 533 patients undergoing percutaneous femoral artery catheterization (1.3 per cent) Of the total group 113 patients had predominant mitral stenosis, and 5 of these developed femoral occlusion (4 4 per cent) Unusually small iliofemoral arteries were found in 5 of the 6 patients who required thrombectomy In addition 2 had atheromatous narrowing and 2 had pre-existing emboli The 5 patients who underwent thrombectomy within 12 hours had good functional results.

Individuals with mitral valve disease weak peripheral pulses, low cardiac output or previous arterial obstruction appear predisposed to arterial occlusion after catheterization Large catheters, prolonged procedures extensive catheter manipulation and excessive pressure to control bleeding should be avoided. Persistent signs of ischemia during a 6 hour observation period after catheterization are an indication for early arterial exploration.

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Coronary risk factors in Northern India

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In recent years coronary heart disease has become of increasingly recognized importance in northern India, where it is seen chiefly among sedentary males of above average income. In the Punjab the usual diet is largely vegetarian and is moderately rich in saturated fat either in the form of "ghee" which is derived from cholesterol containing butter or a substitute for "ghee" which is made from highly saturated hydrogenated cholesterol-free vegetable oils. The chief dietary sources of cholesterol in the West—eggs and meat—comprise a minor part of the Punjabi diet, with considerable individual variation. In the course of an epidemiologic study of Punjabi people, it is thus possible to observe the effect of varying cholesterol content in a diet moderately high in saturated fats.

Studies have shown that occupations involving regular heavy physical exertion are associated with lower levels of serum cholesterol[-4] and a lower prevalence of coronary heart disease.[-4] Such observations are pertinent to a matter of current interest the value of a short period of daily physical exercise as a protective factor in persons with predominantly sedentary occupation. The cultural patterns of Punjabi people have permitted some elucidation of this question also.

Based on the premise that serum cholesterol is of predictive value with regard to the development of coronary heart disease[7,4] this study was designed to investigate the role of habitus diet, daily exercise and certain other factors on serum cholesterol levels.

Methods

This investigation was confined to sedentary males of 30 to 59 years of age. Observations were made at the subjects' places of work by a team of the authors and field assistants, according to a predetermined protocol. The subjects consisted primarily of lawyers and employees of a large bank. These groups were felt to be representative of sedentary male Punjabis. At each site visited by the team all males were included for the study who were residents of the Punjab primarily sedentary in occupation within the age limits as specified and willing to permit a venous blood sample to be drawn. Each subject had a brief medical

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history taken and physical examination performed Note was made of gastrointestinal symptoms from which it was concluded that in this group chronic diarrhea was uncommon (of the 175 subjects only 4 admitted to mild frequency of stools)

The subjects were asked to describe in detail their average daily diet and also the amount of each type of food purchased per week The remarkable uniformity of the Punjabi diet from day to day and the reliance on natural foods rather than commercial preparations made the dietary analysis simpler and probably more reliable than would be the case in a Western diet Based on both daily and weekly dietary data a mean figure was calculated of the daily consumption of total calories carbohydrates, fat (saturated and polyunsaturated) protein cholesterol and sugar

As an estimate of general nutritional status the hemoglobin and serum proteins were determined and were found to be within or just above normal range for Western adult males.* Hemoglobin was measured by colorimeter and serum protein by Benedict s biuret method adapted from Henry and associates[10] Blood sugar was estimated by the Nelson-Somogyi method[11] Serum cholesterol was determined by a modification of the Kiliani Zlatis Zak procedure[12] controlled by a known standard reagent† of 190 mg per 100 ml

Each subject had a 12 lead resting electrocardiogram Relative weight was calculated by dividing the subject s weight by the midpoint of the desirable weight of males of that height according to tables prepared by the Metropolitan Life Insurance Company[13]

An inquiry was made of exercise performed before and after working hours and quantitated in terms of miles walked or cycled per day since it was found that the exercise carried out by members of this group was almost exclusively either cycling or walking

Results

A summary of pertinent data is presented in Table I The prevalence of clinical coronary heart disease and abnormal electrocardiograms was small and did not justify separate analysis.

Regular daily physical exercise before or after otherwise sedentary working hours was found to have negligible influence on the serum cholesterol (correlation coefficient = −0 01)

Serum cholesterol was more highly correlated with relative weight than with any of the other factors studied with a correlation coefficient of 0 38 corresponding to a p value of less than 0 01 (two-tailed)

The serum cholesterol levels were found to have no notable positive correlation to any of the dietary constituents except to the amount of cholesterol in the diet where a significant correlation existed (correlation coefficient = 0 18 p = 0 02) The relationship of dietary cholesterol to serum cholesterol was further analyzed (Table II) and it was found that men consuming less than 100 mg of cholesterol daily had a mean serum cholesterol level of 181 mg per cent while those consuming 200 mg or more of cholesterol in the diet had a mean cholesterol level of 203 mg per cent. This difference was found to be significant (p = 0 01 two-tailed t test)

It is noteworthy that the serum cholesterol had a significant negative correlation with dietary sugar intake (correlation coefficient = −0 17)

The percentage of calories derived from fat showed little variation in this study The proportion of fats which were polyunsaturated also did not vary to any great extent (the P/S ratio was 0 1 S D 0 04) It was therefore not possible to observe the effect of polyunsaturated fat on serum cholesterol levels.

Of the various factors analyzed those having a significant positive correlation with serum cholesterol were age income relative weight and dietary cholesterol The relationship of serum cholesterol to relative weight and dietary cholesterol is shown in Table III Those individuals with relative weight of 100 or less who ingested less than 100 mg of cholesterol per day had a mean serum cholesterol of 168 mg per cent. Those with relative weights greater than 100 who also ate more than 100 mg a day had a mean serum cholesterol of 203 mg per cent If relative weight was over 100 the amount of di[illegible]rol

*Hemoglobin Mean 15.1 Gm., S.D. 1 6. Total serum protein Mean 8.1 Gm., S.D. 0.7; serum albumin mean 5.3 Gm., S.D. 0.5.
†"Choles-trol. Dade Reagents, Inc., Miami, Fla.

made no appreciable difference. Relative weight appeared to have a greater effect at lower levels of cholesterol consumption

In view of the probably interdependence of the variables studied, those variables which appeared most important were analyzed by a multivariate regression technique (Table IV) It appears from this analysis that, of these variables, those affecting serum cholesterol are income (p = 0 05) relative weight (p = 0 001) and dietary cholesterol (p = 0.05) The regression coefficient of 0 03 for dietary cholesterol indicates a change of serum cholesterol of 3 units for every 100 units of change in dietary cholesterol. The estimate of the regression coefficient of serum cholesterol on dietary cholesterol is probably somewhat less than it would be if the dietary factors were measured rather than estimated from the interview [13] In other words, dietary cholesterol may play a greater role than it would appear to play from this type of statistical analysis.

Also worthy of note is the fact that all of the six variables together explain only 24

Table I Summary of data

Variable	No. of individuals	Mean	Standard deviation	Correlation coefficient with serum cholesterol
Age (yr)	175	40 1	7 96	0 12
Physical activity				
(miles per day)	175	1 97	3 4	−0 01
Income (rupees/month)	175	520 3	331 1	0 24
Relative weight	175	100 4	14 1	0 38*
Serum cholesterol	175	186 0	38 9	1 00
Dietary constituents per day				
Protein (Gm.)	175	91 0	34 7	−0 03
Carbohydrate (Gm.)	175	401 6	129 6	−0 14
Sugar (Gm.)	175	50 2	30 2	−0 17†
Total fat (Gm.)	175	94 7	49 1	−0 03
Sat. fat (Gm.)	175	86 4	44 8	−0 03
Polyunsat. fat (Gm.)	175	8 4	5 8	−0 01
Cholesterol (mg)	175	125 6	182 4	0 18†
Total calories	175	2 844	914	−0 06
% of calories derived from total fats	175	29 5	9 8	0 03

*Two-tailed significance (p) <0 01.
†Two-tailed significance (p) <0 05.

Table II Cholesterol consumption in relation to serum cholesterol levels

	Dietary cholesterol (mg./day)		
	<100	100 to 199	200 or >
No. of individuals	122	19	34
Cholesterol consumption (mg per day—mean) (S.D)	36 3 (26 7)	130 4 (29 1)	432 5 (213 3)
Serum cholesterol (mg %—mean) (S.D)	181 (40)	188 (30)	203 (37)

history taken and physical examination performed Note was made of gastrointestinal symptoms from which it was concluded that in this group chronic diarrhea was uncommon (of the 175 subjects only 4 admitted to mild frequency of stools)

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Of the various factors analyzed those having a significant positive correlation with serum cholesterol were age income relative weight and dietary cholesterol The relationship of serum cholesterol to relative weight and dietary cholesterol is shown in Table III Those individuals with relative weight of 100 or less who ingested less than 100 mg of cholesterol per day had a mean serum cholesterol of 168 mg per cent. Those with relative weights greater than 100 who also ate more than 100 mg a day had a mean serum cholesterol of 203 mg per cent If relative weight was over 100 the amount of dietary cholesterol

*Hemoglobin Mean 15.1 Gm., S.D. 1 6. Total serum protein Mean 8.1 Gm., S.D. 0.7; serum albumin mean 5.3 Gm., S.D. 0.5.

†Chol-e-trol. Dade Reagents, Inc., Miami, Fla.

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portance than limiting dietary cholesterol in controlling serum cholesterol levels. However the mechanism of action of polyunsaturated fats may be in part one of preventing absorption and promoting fecal excretion of both exogenous and endogenous cholesterol [33] Thus, it may be that reduction of cholesterol in the diet and the fat-controlled diet both have the same result—one of reducing the amount of cholesterol absorbed from the intestinal tract

Obesity The finding in the present study of the correlation of high relative weight with serum cholesterol does not appear to have been widely reported although this observation was also made by Padmavati and associates[34] in Delhi It is suggested from the data of the present study that the effect of weight on serum cholesterol may be more apparent on a low cholesterol diet (Table III) The high cholesterol diet of the average American could mask the hypercholesterolemic effect of obesity In the National Diet Heart Study the largest drops in serum cholesterol were observed in men with the largest decrease in weight from the base-line period [31] In the management of hyperlipoproteinemias it has been found that in Types III IV and V the response of the hyperlipoproteinemia (and hypercholesterolemia) is very favorable to weight reduction to an ideal body weight, although reduction in dietary cholesterol also has a favorable effect. Type II or hyper beta lipoproteinemia may arise in some persons simply from excesses of dietary cholesterol and saturated fats [35]

Exercise There is evidence from a variety of sources that daily physical exercise may limit the development of clinical coronary heart disease [1,2,4 6] However the present study suggests that in otherwise sedentary males moderate regular daily exercise does not exert a notable protective effect through the mechanism of decrease in serum cholesterol

Dietary sugar Yudkin has expressed the view that a high intake of sugar in the diet plays a large part in the etiology of atherosclerotic disease [36,37] In the present study as well as in other published studies [38-40] there is not a positive correlation between dietary sugar and serum cholesterol levels in fact in this study there was a significant negative correlation of dietary sugar and serum cholesterol suggesting that dietary sugar reduces serum cholesterol.

Summary

A study was made of 175 sedentary male lawyers and bank employees between 40 and 60 years of age in Punjab India to observe the relationship of diet body build, and directed daily exercise to serum cholesterol levels. Dietary analysis was made from interviews. The consumption of saturated fat was found to be moderately high (30 per cent of calories) and of cholesterol low (mean 126 mg per day) Of dietary factors only cholesterol was positively correlated to a significant degree with serum cholesterol The effect of dietary cholesterol was small with 3 mg per cent change in serum cholesterol per 100 mg of change in dietary cholesterol Relative body weight appeared to have more influence than dietary factors on serum cholesterol Short periods of daily exercise had no significant effect on serum cholesterol levels. Dietary sugar was found to be negatively correlated with serum cholesterol

We are grateful for the statistical assistance of Mr Michael Butterworth.

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Aneurysm of the membranous ventricular septum

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Aneurysm of the membranous ventricular septum is an uncommon anomaly which has been generally diagnosed only at autopsy in the past.[1] The advent of angiocardiography, however, has made possible its diagnosis during life.[2-4] With the increasing recognition of its association with other cardiovascular defects[1,3-7] and its role in the production of significant anatomic, electrocardiographic, and hemodynamic changes,[1,8-11] an awareness of the helpful clues that could lead to its eventual diagnosis by angiocardiography[12] is important. It is the purpose of this communication to report four cases of this anomaly diagnosed during life by angiocardiography at the University of Mississippi Medical Center within the past two years.

Case reports

Patient 1. A 24-year-old Caucasian man with known heart murmur since birth had cardiac catheterization without angiocardiography at 18 years of age which revealed a small ventricular septal defect. A year later he developed vague chest pains which eventually led to his admission for a repeat cardiac catheterization. On examination, a systolic thrill at the left sternal border was felt. There was a grade 3-4/6 pansystolic murmur with a crescendo-decrescendo configuration (Fig. 1, *A*) at the left lower sternal border with moderate precordial transmission. The second heart sound was single and of normal intensity. A third heart sound was present at the apex.

A routine urinalysis and blood count were normal. The chest x-ray revealed a slight prominence of the pulmonary vascular markings and the electrocardiogram (ECG) showed an axis of minus 30 degrees. Cardiac catheterization (Table I) again revealed a left-to-right shunt at the ventricular level. Left ventricular cineangiography (Fig. 2, *A*) showed a thumblike structure protruding into the right ventricle just below the normal aortic valve which filled and emptied with cardiac contractions. A left-to-right shunt through a defect at the superior portion of the dome of this structure was present. The coronary arteries appeared normal. Following discharge the patient was asymptomatic. No surgery was contemplated.

Patient 2. A 30-year-old Caucasian man with known heart murmur since birth was admitted to the hospital for cardiac catheterization following occasional chest pains and a syncopal episode while straining during defecation (the latter is likely similar to Valsalva maneuver resulting in syncope) the preceding month, which made him concerned with his heart condition. Examination revealed a peculiar narrowing of the peripheral fissures of the eyes. Pectus carinatum was present (also present in a grandfather and a son). A grade 3/6 harsh

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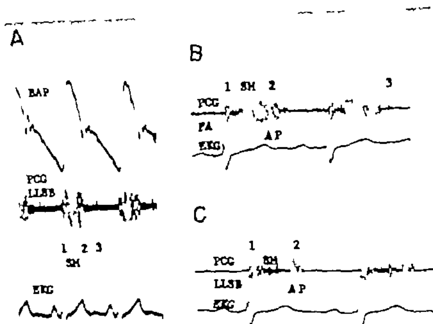


Fig. 1. *A*, Phonocardiogram (*PCG*) in Patient 1 taken at the left lower sternal border (*LLSB*) showing a systolic murmur (*SM*) with a crescendo-decrescendo character. Note simultaneous brachial artery pressure (*BAP*). *B*, Phonocardiogram (*PCG*) in Patient 3 showing somewhat crescendo-decrescendo systolic murmur (*SM*) at the pulmonic area (*PA*) with late systolic accentuation. Note the presence of a third heart sound or an early diastolic murmur. *C*, Note pansystolic murmur at the left lower sternal border (*LLSB*) in the same patient (No. 3).

Table I. Cardiac catheterization

Patient no.	SVC	IVC	RA	RA	RV	RV	PA	PA	PA	LV	LV	Aorta	Aorta	Aorta	Cardiac index (L./min./M.²)
	% O_2 Sat.	% O_2 Sat.	Mean pressure (mm. Hg)	% O_2 Sat.	Pressure S/D (mm. Hg)	% O_2 Sat.	Pressure (mm. Hg) S/D	Pressure (mm. Hg) Mean	% O_2 Sat.	Pressure S/D (mm. Hg)	% O_2 Sat.	Pressure (mm. Hg) S/D	Pressure (mm. Hg) Mean	% O_2 Sat.	
1	74	72	4	72	21/6	81	21/10	14	79	105/8	98	105/70	85	—	4.8
2	69	78	6	73	22/6	78	22/10	12	79	120/10	—	115/80	100	97	5.3
3	66	—	1	69	24/1	73	21/6	10	73	89/2	96	85/54	75	—	2.9
4	71	82	2.5	73	25/3	75	23/10	15	79	105/8	99	105/70	85	—	3.8

Oxygen saturation as determined by oximetry.
Abbreviations: SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; PA, pulmonary artery; LV, left ventricle; Sat, saturation; S/D, systolic/diastolic.

medium-pitched pansystolic murmur with late systolic accentuation (Fig. 3) was present along the left sternal border with slight precordial transmission. The second heart sound was normally split and not accentuated.

Routine urinalysis, blood count, chest x-ray and ECG were normal. On cardiac catheterization (Table I) a very small left-to-right shunt at the ventricular level and a 10 mm. Hg gradient across the pulmonic valve were present. Left ventricular cineangiography (Fig. 2, *B*) revealed a pouchlike structure protruding into the right ventricle just below the normal aortic valve which filled and emptied with cardiac contractions. A left-to-right

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A routine urinalysis and blood count were normal. The chest x ray revealed a slight prominence of the pulmonary vascular markings and the electrocardiogram (ECG) showed an axis of minus 30 degrees. Cardiac catheterization (Table I) again revealed a left to-right shunt at the ventricular level Left ventricular cineangiography (Fig 2, A) showed a thumblike structure protruding into the right ventricle just below the normal aortic valve which filled and emptied with cardiac contractions A left-to-right shunt through a defect at the superior portion of the dome of this structure was present. The coronary arteries ppeared normal Following discharge the patient was asymptomatic. No surgery was contemplated

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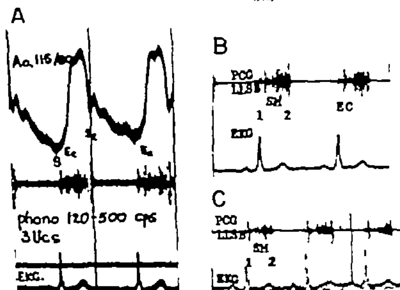


Fig. 3. Phonocardiogram (*PCG*) in Patient 2. *A*. Taken at the third left intercostal space (*3 LICS*) along the sternal border with simultaneous aortic pressure (*A*). Note systolic murmur (*SM*) with somewhat crescendo-decrescendo character and the ejection click (*EC*). *B*. Taken at the left lower sternal border (*LLSB*) prior to the administration of amyl nitrite showing pansystolic murmur with late systolic accentuation. *C*. Note the decrease in intensity of the murmur 40 seconds following the administration of amyl nitrite as would be expected in ventricular septal defects. (Paper speed of 50 mm. per second in *B* and 25 mm. per second in *C*)

inflow murmur or third heart sound related to some increase in blood flow across the mitral valve. The second heart sound was moderately split, not fixed, and not accentuated.

The laboratory studies performed were in keeping with viral infection. The chest x-ray showed slight increase in the pulmonary vascular markings and the ECG revealed an axis of minus 30 degrees with a suggestion of slight left ventricular hypertrophy. Cardiac catheterization (Table I) revealed normal pressures and oxygen saturations. Left ventricular cineangiography (Fig. 2, *C*) showed localized bulging of the membranous portion of the ventricular septum toward the right ventricle just below the normal aortic cusps. A left-to-right shunt through a small defect at the superior portion of the dome of the outpouching was present. The pouch-like structure partially emptied with cardiac contractions with its lower portion persistently retaining part of the radiopaque material and maintaining convexity toward the right ventricle. The patient was discharged in good condition, and will be followed in the cardiac clinic with no surgery contemplated.

Patient 4. A 21-year-old essentially asymptomatic Caucasian man with a heart murmur present since birth was referred to the hospital for cardiac catheterization. Physical examination revealed the presence of a grade 3-4/6 pansystolic murmur at the left sternal border with slight transmission to the axilla. The murmur had a crescendo-decrescendo character at the second and third left intercostal space where a systolic thrill was also felt. There were no other remarkable findings.

A urinalysis, blood count, chest x-ray and ECG were all normal. Cardiac catheterization (Table I) revealed normal pressures and a very small left-to-right shunt at the ventricular level. The left ventricular cineangiogram (Fig. 2, *D*) showed saccular outpouching of the membranous portion of the ventricular septum into the right ventricular cavity immediately below the aortic valve. A small left-to-right shunt through a defect at the upper part of the saccular outpouching was present. The patient was discharged from the hospital with no surgery contemplated.

Discussion

The first description of a ventricular septal aneurysm was attributed to Laennec in 1826 by Lev and Saphir[14] who reviewed the literature up to 1938 and found 70 cases reported to which they added 2 of their own. Yang and associates[12] subsequently put the total number of cases reported up to 1967 to 108 to which they added 2 other cases. In addition to these a few other reports have appeared in the literature.[14-]

Several theories had been proposed to explain the development of the anomaly[12,14,19] however the most plausible is that the aneurysm of the membranous ventricular septum develops in relation to the natural spontaneous closure of a ventricular septal defect. Since the area is weak it

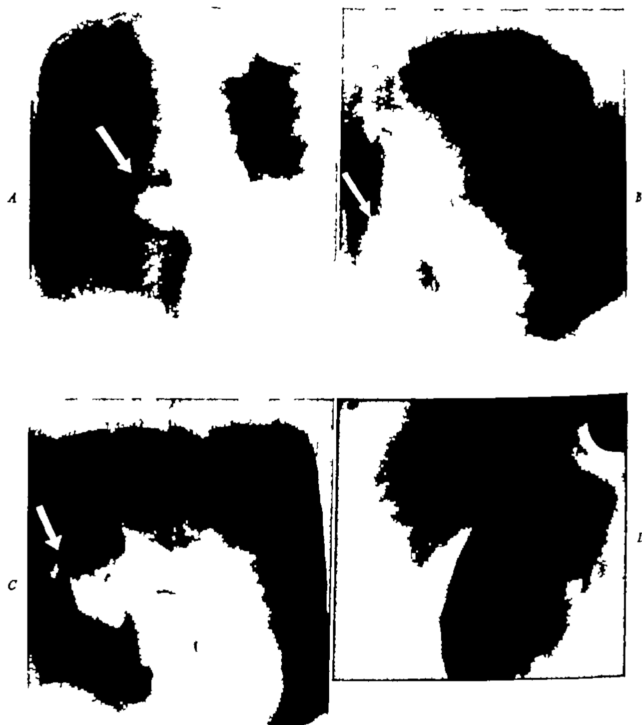


Fig 2 Left ventricular angiocardiogram in the left anterior oblique position showing the aneurysm of the membranous ventricular septum bulging towards the right ventricle just below the aortic valve in (*A*) Patient 1 (*B*) Patient 2 (*C*) Patient 3 and (*D*) Patient 4 Note the left to-right shunt through a small ventricular septal defect at the superior part of the aneurysm in all four cases (arrow)

shunt through a small defect at the superior portion of the dome of this structure was noted. The coronary arteries were normal. Since discharge from the hospital the patient has been asymptomatic. No surgery was planned.

Patient 3 A 15-year-old Negro boy with the sickle cell trait was admitted to the hospital for a suspected viral infection. On examination, a grade 3/6 ejection-type systolic murmur with late systolic accentuation was noted at the pulmonic area with some precordial transmission. A grade 2/6 pansystolic murmur was also present at the left lower sternal border. Phonocardiography confirmed the murmurs and also revealed either a third heart sound or a short early diastolic murmur (Fig 1 *B* and *C*) The latter was likely a

rysm may persist. This would explain the absence of a demonstrable ventricular septal defect in some cases of aneurysm of the membranous ventricular septum. At the present time, we feel that surgical intervention is not indicated in asymptomatic patients with essentially benign cardiovascular findings. These patients, however should be on prophylaxis for bacterial endocarditis as in other congenital heart diseases. Certainly a long-term follow-up and future re-evaluation of these patients would be needed if we are to know more of the natural course of this anomaly and thereby be able to manage it more appropriately

Summary

Four cases of aneurysm of the membranous ventricular septum with associated ventricular septal defects diagnosed by left ventricular angiocardiography are reported and discussed in relation to the pertinent literature.

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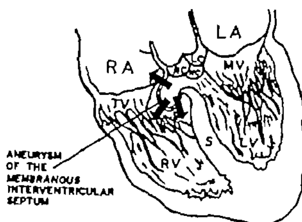


Fig. 4 Diagram of the heart as viewed in a left anterior oblique position showing the relative position of the ventricular septal aneurysm and the possible sites into which it may bulge or rupture (arrows) Symbols *RA* Right atrium *LA* left atrium *RC* right coronary cusp of aortic valve *LC* left coronary cusp of aortic valve *NC* noncoronary cusp of aortic valve *TV* tricuspid valve *MV* mitral valve, *RV* right ventricle *LV* left ventricle, and *S* muscular septum.

bulges into the right ventricular cavity as a result of the higher left ventricular pressure Aneurysms have been observed however to protrude into other areas such as the right atrium and the exterior of the heart or to displace the other cardiac chambers[1, 10, 13, 20, 21] (Fig 4)

The only certain way of diagnosing the anomaly is by selective angiocardiography which would show an outpouching below the root of the aorta Clinically the manifestations would be those of the associated defects. In instances where the aneurysm extends to the exterior of the heart or displaces any cardiac chamber this may be visualized radiologically[1, 21] The ECG could be of help mainly in that arrhythmias and other changes have been described in several cases. In one instance, an abnormal P axis resulted from the displacement of the right atrium and sinus node by the huge aneurysm[1]

The aneurysm has been associated with morbidity or death in some instances[11, 13, 21] It has been observed to rupture and cause death[13] to be the site of thrombus formation or endocarditis,[13, 14] to cause obstruction of the right and left ventricular outflow tracts,[8, 9, 18, 19] to be associated with valvular disease particularly aortic insufficiency[...] and ventricular septal defects, atrial septal defects endocardial cushion defects, transposition of the great vessels and others[1, 3, 8, 9, 10, 13, 14, 19] and also with varying types of arrhythmias and other electrocardiographic changes[1, 9, 10, 13, 21] The latter may not be surprising considering the intimate relationship of the membranous septum with the bundle of His.[7]

The presence of a murmur in addition to a high index of suspicion can be helpful in eventually suspecting the anomaly as it could suggest the other associated lesions, although murmurs that could be attributed only to the aneurysm have been described[4, 8, 21] *As the aneurysm frequently* impinges on the right ventricular outflow tract an ejection type systolic murmur at the pulmonic area could be expected as in Cases 1 3 and 4 and that of Das and associates.[8] The late accentuation of the systolic murmur in Cases 2 and 3 and in other reported cases[4, 21] may be a result of the impingement of the aneurysm into the right ventricular outflow tract during late systole causing a functional state of pulmonary stenosis Hemodynamically this has been observed to exist[8, 9] and is probably present to a slight degree in Case 2 where a gradient of 10 mm Hg was demonstrated However the presence of an ejection click in the phonocardiogram (Fig 3) in this particular case may suggest more of an obstruction at the valvular rather than at the infundibular level The absence of a gradient across the pulmonic valve in the presence of an ejection systolic murmur in Cases 1 and 4 would suggest that the aneurysm was not obstructing the right ventricular outflow tract although its presence was sufficient enough to produce a murmur It is probable that the combination of a pansystolic murmur along the left sternal border and an ejection systolic murmur at the base (especially if with late systolic accentuation) may be of value in suspecting the presence of an aneurysm of the membranous ventricular septum.

The course of patients with this anomaly is still very poorly known The experiences of Cornell and Durnin[16] and that of Summerall and co-workers[17] would suggest that the ventricular septal defect may eventually close spontaneously although the aneu-

sm may persist. This would explain the sence of a demonstrable ventricular sep-l defect in some cases of aneurysm of the embranous ventricular septum. At the esent time we feel that surgical inter ention is not indicated in asymptomatic atients with essentially benign cardio-ascular findings. These patients, however, ould be on prophylaxis for bacterial endo-arditis as in other congenital heart dis-ases. Certainly a long-term follow-up and uture re-evaluation of these patients would e needed if we are to know more of the atural course of this anomaly and thereby e able to manage it more appropriately

Summary

Four cases of aneurysm of the mem ranous ventricular septum with associated entricular septal defects diagnosed by left entricular angiocardiography are reported nd discussed in relation to the pertinent terature

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Results and correlations of multistage exercise tests in a group of clinically normal business executives

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Long term studies of clinically healthy individuals have demonstrated that those in whom S-T-segment depression develops following moderate levels of exercise (Master s two-step test) have an increased risk of clinical coronary arterial disease [1,2] More recently several authors have recommended testing with much higher levels of exercise in part to increase the diagnostic yield in these individuals [3-4] However the significance of S-T-segment changes during and after strenuous exercise is still uncertain because a long term follow up of subjects with abnormal electrocardiographic exercise responses is not always available

Several prospective epidemiologic studies have shown that many factors such as hypertension diabetes high cholesterol levels, smoking obesity and family background are associated with an increased risk of ischemic heart disease [6,7] However few authors[8-10] have systematically examined the interrelationship of the results of strenuous exercise tests and the presence of these coronary risk factors The purpose of this study was to attempt to find such correlations in a group of middle-aged healthy business executives.

Material and methods

As part of a general health evaluation 91 healthy business executives (mean age 44 years, range 30 to 60 years) performed a standardized multistage exercise test as described by Doan and associates.[4] Medical and family history were obtained in all subjects as well as a complete physical examination prior to the exercise test. Particular attention was paid to a personal history of cigarette smoking and a family history of heart disease. None of the subjects had symptoms or signs of heart disease Height and weight were measured and the degree of overweight was estimated by using the tables of the Metropolitan Life Insurance Company of New York Spirometry was performed by standard techniques. A 12 lead resting electrocardiogram (ECG) was obtained and interpreted by the authors. Complete blood counts, urinalysis and a chest film were obtained

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Serum cholesterol,[11] uric acid [12] and two-hour post-Glucola blood glucose[13] determinations were carried out. The accuracy of the last three measurements was established by the following coefficients of variation (100 × standard deviation of the difference/mean) cholesterol 4.6 per cent uric acid 5.0 per cent glucose, 2.0 per cent.

Electrographic monitoring and recording (direct writer* paper speed 25 mm. per second) were accomplished with a slight modification of the precordial ECG described by Aharquez and associates.[14] The electrodes were placed as follows RA on the forehead, LA on the ensiform process, RL on the V_{5R} position LL on the V_5 position and the V lead on the V_4 position. Recordings were made with the unipolar leads aVR, aVL, aVF and V. Exercise on the treadmill† was continuous and consisted of three-minute stages of gradually increasing speed and grade. Blood pressures at rest, during each stage of exercise and in the recovery period were obtained with a mercury sphygmomanometer by the cuff method with the subjects in the standing and walking positions. Participants were encouraged to do as much as they could. Endurance time was defined as the duration of the treadmill exercise. A physician was in attendance during the testing procedure. Immediately prior to the exercise, a continuous recording of the precordial ECG was made during 45 seconds of hyperventilation and a 15 second Valsalva maneuver. The Valsalva ratio was obtained by dividing the longest R-R interval by the shortest R-R interval in the period immediately following the Valsalva maneuver as described by Levin.

Interpretation of exercise ECG's. Tracings were interpreted independently by two of us (A.N.C. and J.F.M.). When disagreements occurred on a particular tracing the tracing was reviewed jointly. This occurred on 6 of the 91 tracings.

An abnormal response was defined as at least 1 mm. S-T-segment depression in any lead during or after exercise, with a flat or down ard sloping of the S-T segment not present during rest, hyperventilation or Valsalva maneuvers (vide infra). Figs. 1 and 2 illustrate a normal and an abnormal response, respectively.

Labile T wave changes present a difficulty in the interpretation of the tracings. We use the hyperventilation and Valsalva maneuvers to separate those individuals with labile T wave changes from those with ischemic ST T changes. Several authors[17, 18] have shown that hyperventilation and orthostatic-induced T-wave changes were found in healthy and younger individuals and were not related to ischemic heart disease. Fig. 3 illustrates the similarities between the ST T-wave changes induced by hyperventilation and those present during and after exercise. The resemblance becomes more marked if the J-point depression due to increased heart rate is taken into account. We have somewhat arbitrarily classified tracings with ST T changes during and after exercise in the normal category if similar changes were induced by hyperventilation or occurred with changes in position. Previous observations demonstrated [9] that similar considerations may apply to the ST T-wave changes seen during the Valsalva maneuver. An example of Valsalva induced ST T-wave changes and similar changes seen in the recovery period are shown in Fig. 4. This tracing was interpreted as showing labile ST T changes and was classified as normal.

The data were keypunched onto IBM cards and means standard deviations (S.D.) standard error of the mean (S.E.M.) correlation coefficients (r) and the Student t test were carried out with standard formulas on the IBM 7094 computer at the Biological Sciences Computation Center of the University of Chicago.

Results

Abnormal responses. Of the 91 subjects, 11 (12 per cent) developed abnormal S-T-segment depression as previously defined and were called positive responders. On that basis, the population studies were divided into two groups, namely positive responders and nonresponders.

Physical characteristics and coronary risk factors. Table I details the mean values, standard errors of the mean and differences between the two groups in age physical characteristics, and coronary risk factors

*Hewlett Packard, Model No. 1511A.
†Quinton Instruments, Model No. 18-49EL.

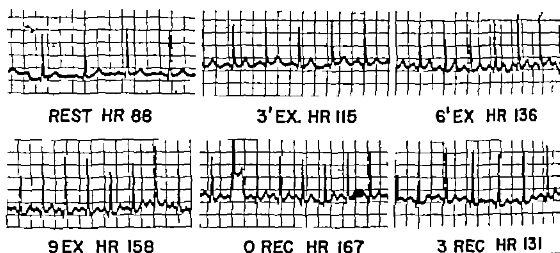


Fig *1* Normal ECG response to the multistage exercise test in a 43-year-old man. *H R* Heart rate 3' EX, third minute exercise 3 REC, third minute after cessation of exercise (recovery)

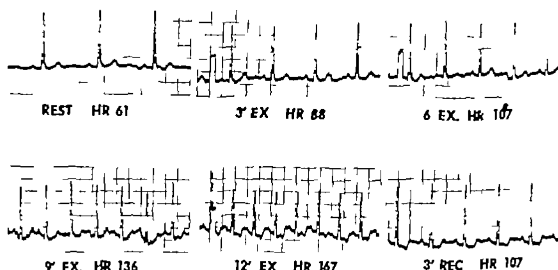


Fig *2* Abnormal ECG response to the multistage exercise test due to S-T-segment depression of more than 1 mm with downward sloping in a 52 year-old man.

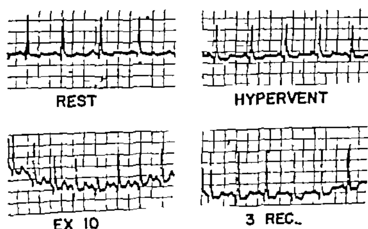


Fig *3* Comparison between ST T changes induced by hyperventilation and those present during the recovery period in a 47-year-old man (see text).

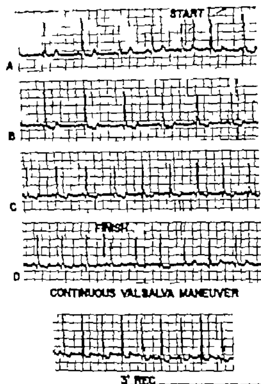


Fig. 4 Comparison of ST T changes induced by the Valsalva maneuver (continuous strip, A to D row) and the ST T changes present during the recovery period in 39-year-old man (see text).

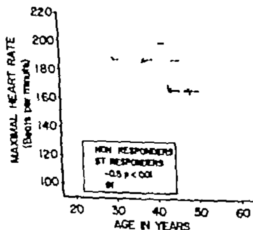


Fig. 5 Relationship between maximal heart rate attained in the treadmill test and age in the study population.

The only significant difference between the two groups was that the individuals with abnormal ST T-wave changes were older than the nonresponders (51 versus 43 years, respectively p <0 001)

The participants were subdivided according to the number of coronary risk factors present. Among 43 executives with no more than one coronary risk factor 4 (11 per cent) were positive responders. A similar frequency of positive responders, 7 of 48 (17 per cent) was found in the other participants who had 2 or more coronary risk factors.

Electrocardiographic and physiologic data (*Table II*) ECG abnormalities at rest were present in 5 of the nonresponders and 3 of the responders (6 and 27 per cent, respectively chi square 4.8 p <0.05) In the positive responders, left-axis deviation (more than −30 degrees) was present in two subjects, and first-degree A V block in another Among the nonresponders, left axis deviation was found in four subjects, associated with nonspecific T wave changes in one of these, while another had evidence for left ventricular hypertrophy

Nonresponders had faster resting heart rates than the responders (81 versus 71 beats per minute p <0 05) There were no differences between the groups in resting blood pressure and Valsalva ratio.

Exercise performance As shown in Table II no difference was found between nonresponders and responders in endurance time (11 1 minutes for both groups) maximal heart rate (178 and 169 beats per minute respectively) maximal blood pressure, and the appearance of premature beats during exercise.

Correlations with age The maximal heart rate attained during exercise is plotted against the age of the subjects in Fig 5 The maximal heart rate decreased with advancing age, with a significant negative correlation coefficient (r = −0.52 p <0 001) It was notable that 13 individuals between 30 and 45 years of age had maximal heart rates in excess of 200 beats per minute.

Although a significant negative correlation was found between maximal heart rate and age no correlation between resting heart rate and age was demonstrated.

Endurance time, a measure of physical fitness, was found to have a significant

Table I Physical characteristics and coronary risk factors in 91 healthy business executives (mean ± S E M)

Variables	Nonresponders (n = 80)	Responders (n = 11)	p
Age (yr)	43 2 ± 0 8	51 0 ± 1 7	<0 001
Height (cm)	155 5 ± 0 5	156 9 ± 1 7	ns
Weight (kg)	83 6 ± 1 3	83 3 ± 3 1	ns
% Overweight	15 9 ± 1 4	14 5 ± 2 8	ns
Cholesterol (mg %)	214 0 ± 4 1	210 9 ± 8 3	ns
Uric acid (mg %)	5 8 ± 0 1	5 6 ± 0 3	ns
2 hr post-Glucola (mg %)	108 ± 3 7	98 ± 5 7	ns
1 sec expiratory flow (% of vital capacity)	77 7 ± 1 8	73 9 ± 1 7	ns
Cigarette smoking (%)	26	18	ns
Positive family history (%)	55	36	ns

Table II Electrocardiographic and physiologic data in 91 healthy business executives (mean ± S E M)

Parameters	Nonresponders (n = 80)	Responders (n = 11)	p
Abnormal resting 12 lead ECG (%)	6	27	<0 05
Resting heart rate (beats/min.)	81 ± 1 4	71 ± 2 7	<0 05
Resting systolic blood pressure (mm. Hg)	120 ± 1 1	117 ± 3 7	ns
Resting diastolic blood pressure (mm Hg)	82 ± 1 0	74 ± 3 7	ns
Valsalva ratio	1 8 ± 0 4	1 6 ± 0 9	ns
Endurance time (min)	11 1 ± 0 2	11 1 ± 0 7	ns
Maximal heart rate (beats/min.)	178 ± 1 9	169 ± 5 3	ns
Max. systolic blood pressure (mm Hg)	184 ± 1 7	179 ± 5 4	ns
Max. diastolic blood pressure (mm. Hg)	81 ± 1 4	73 ± 3 2	ns
Percentage individuals who develop premature beats during exercise (%)	19	9	ns

*See text

negative correlation with age (r = −0 3 p <0 01)

The only other significant correlations with age were the two-hour p c glucose r = 0.22 p < 0 05 the 1 second expiratory flow r = −0 27 p <0 01 and the Valsalva ratio r = −0 26 p <0 05

Discussion

The problems of instrumentation technique and interpretation of the exercise ECG have been reviewed by Blackburn and associates[19] Unresolved problems regarding standardization of leads systems types of exercise (treadmill versus bicycle continuous versus intermittent maximal versus submaximal) and recording apparatus still exist. Although measurements of the S-T-segment slope have been suggested[21] for the differentiation between normal and abnormal responses those measurements are of no value in cases of neurocirculatory asthenia and labile ST T-wave changes The use of hyperventilation and Valsalva maneuvers may be of value in discriminating between organic and functional ST T-wave changes as discussed under Methods The discriminatory value of the hyperventilation and Valsalva maneuver remains to be proven Clearly however the inclusion of these additional techniques is an important adjunct to any

electrocardiographic evaluation of exercise. In addition problems of muscular noise and wandering baseline further complicate analysis of the exercise ECG. Recently attempts have been made to solve some of these problems by utilizing modern techniques of data processing.[22,23] However until agreement is reached regarding methodology and interpretation of the exercise ECG and until computer techniques are further refined current methods and empirical analysis will continue to be utilized.

It is known that the maximal heart rate attained during exercise declines with age. Lester and associates[24] recently confirmed observations made by Robinson[25] 30 years ago and reported correlation coefficients between maximal heart rate and age of −0.541 and −0.578 for a group of trained and untrained individuals. This compares favorably with the correlation coefficient found in this study of −0.541. The reasons for the decrease in maximal heart rate are unknown.

Although Blackburn and associates[26] found a large amount of interobserver variation in the interpretation of exercise ECG's the frequency of 12 per cent of abnormal responses in this study is in the same range as that reported in the literature. Using a 1 mm. S-T–segmental depression as a positive criterion Doan and associates[4] found 26 responders out of 225 Y.M.C.A. men (11.5 per cent). With comparable techniques others[2] found a prevalence rate of 5.2 per cent. Higher frequencies were reported by Bellet and associates and Berkson and co-workers 25 and 20 per cent respectively. The apparent reasons for these increased rates may be the use of a 0.5 mm. S-T–segment depression, T wave inversions, and premature beats as criteria for a positive response. In support of this interpretation is a recent study of 912 healthy Chinese men by Li and associates,[27] who found an 8 per cent frequency on the basis of a 1 mm. S-T depression. However this rate would have been increased to 18 per cent if the criterion for a positive response were a 0.5 mm. S-T–segmental depression.

In studying the relationships between submaximal and maximal exercise test results and other presumed factors in the development of coronary arterial disease, Bellet and associates[4] found a significant relationship between positive exercise tests and elevated serum cholesterol levels. Berkson and associates showed that individuals with one or more coronary risk factors had a higher incidence of positive response to submaximal exercise. In the three-year follow up study from Bruce's laboratory[18] consistent responders were found to be older, shorter, with a lower vital capacity and a reduced endurance time than nonresponders. Although no relationship was found between age and height-adjusted serum lipids and abnormal S-T responses for the entire population studied significant differences in serum lipids and blood pressure were found between 13 men who reverted from positive to negative and 8 men who converted from negative to positive S-T patterns.

The findings in this study are somewhat at variance with those discussed previously in that no relationship between coronary risk factors and positive responses was found. In our small sample the appearance of ECG abnormalities at rest and during exercise in the older age groups suggests either that these changes are due to the aging process or that they may indeed represent latent coronary artery disease. Only the long term follow-up of these and similar groups of subjects will demonstrate which of these two possibilities is correct. At that time, the predictive value of the maximal exercise test for the early detection of coronary arterial disease in clinically healthy individuals will be established. Until such information becomes available perhaps caution should be advised in labeling abnormal responses as indicative of latent coronary arterial disease.

Summary

Multistage treadmill exercise tests were performed on 91 healthy business executives. Eleven of these subjects exhibited abnormal S-T–segment responses. Although no correlation was found between abnormal exercise responses and the coronary risk factors, the abnormal responders were older and had more abnormalities in the resting ECG. The predictive value of the maximal exercise test will be determined in the long term follow-up of these individuals.

Table I Physical characteristics and coronary risk factors in 91 healthy business executives (mean ± S.E.M.)

Variables	Nonresponders (n = 80)	Responders (n = 11)	p
Age (yr.)	43.2 ± 0.8	51.0 ± 1.7	<0.001
Height (cm.)	155.5 ± 0.5	156.9 ± 1.7	ns
Weight (Kg.)	83.6 ± 1.3	83.3 ± 3.1	ns
% Overweight	15.9 ± 1.4	14.5 ± 2.8	ns
Cholesterol (mg. %)	214.0 ± 4.1	210.9 ± 8.3	ns
Uric acid (mg. %)	5.8 ± 0.1	5.6 ± 0.3	ns
2 hr. post-Glucola (mg. %)	108 ± 3.7	98 ± 5.7	ns
1 sec. expiratory flow (% of vital capacity)	77.7 ± 1.8	73.9 ± 1.7	ns
Cigarette smoking (%)	26	18	ns
Positive family history (%)	55	36	ns

Table II Electrocardiographic and physiologic data in 91 healthy business executives (mean ± S.E.M.)

Parameters	Nonresponders (n = 80)	Responders (n = 11)	p
Abnormal resting 12 lead ECG (%)	6	27	<0.05
Resting heart rate (beats/min.)	81 ± 1.4	71 ± 2.7	<0.05
Resting systolic blood pressure (mm. Hg)	120 ± 1.1	117 ± 3.7	ns
Resting diastolic blood pressure (mm. Hg)	82 ± 1.0	74 ± 3.7	ns
Valsalva ratio	1.8 ± 0.4	1.6 ± 0.9	ns
Endurance time (min.)	11.1 ± 0.2	11.1 ± 0.7	ns
Maximal heart rate (beats/min.)	178 ± 1.9	169 ± 5.3	ns
Max. systolic blood pressure (mm. Hg)	184 ± 1.7	179 ± 5.4	ns
Max. diastolic blood pressure (mm. Hg)	81 ± 1.4	73 ± 3.2	ns
Percentage individuals who develop premature beats during exercise (%)	19	9	ns

*See text.

negative correlation with age ($r = -0.3$, $p < 0.01$).

The only other significant correlations with age were the two-hour p.c. glucose ($r = 0.22$, $p < 0.05$), the 1 second expiratory flow ($r = -0.27$, $p < 0.01$), and the Valsalva ratio ($r = -0.26$, $p < 0.05$).

Discussion

The problems of instrumentation, technique, and interpretation of the exercise ECG have been reviewed by Blackburn and associates.[11] Unresolved problems regarding standardization of leads systems, types of exercise (treadmill versus bicycle, continuous versus intermittent, maximal versus submaximal) and recording apparatus still exist. Although measurements of the S-T-segment slope have been suggested[12] for the differentiation between normal and abnormal responses, those measurements are of no value in cases of neurocirculatory asthenia and labile ST-T-wave changes. The use of hyperventilation and Valsalva maneuvers may be of value in discriminating between organic and functional ST-T-wave changes as discussed under Methods. The discriminatory value of the hyperventilation and Valsalva maneuver remains to be proven. Clearly, however, the inclusion of these additional techniques is an important adjunct to any

Experimental and laboratory reports

P waves and P loops in coronary sinus and left atrial rhythms

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The clinical electrocardiographic criteria of a coronary sinus rhythm (CSR) are generally accepted to be inversion of P waves in Leads II III and aV upright P waves in Lead aV R, and a P R interval of normal duration.[1] A variety of techniques has been used to experimentally reproduce CSR or A V junctional rhythms in both man and animals. However the suggested criteria have not always been reproduced nor have the possible sites of origin of this ectopic rhythm and its supraventricular conducting pathways been definitively determined

Recently Mirowski[2-10] called attention to certain P wave changes which he proposed as diagnostic criteria of a left atrial rhythm (LAR) Other investigators[1-11] have failed to confirm these criteria in experimentally produced LAR The criteria for the diagnosis of CSR and LAR remain varied, and the electrocardiographic P wave changes and P loops often overlap in these two rhythms.[9-11]

The present investigation was undertaken to study the P waves during transvenous pacing with an electrode catheter positioned in specific locations in the great cardiac vein and left atrium. Multiple standard-lead electrocardiograms (ECG s) P loops, and intra-atrial electrograms were utilized in the analysis of these changes. Data will be presented to show that the electrophysiological characteristics of a CSR are identical with and indistinguishable from those of an inferior LAR.

Methods and materials

Studies in dogs Preliminary studies were first conducted in nine dogs, all of whom were in normal sinus rhythm (NSR) with normal atrioventricular conduction. Since body and limb position may affect the contour and amplitude of the P wave all recordings of ECG s and P loops were obtained with the dogs in a standardized supine position and with the limbs parallel to the trunk.

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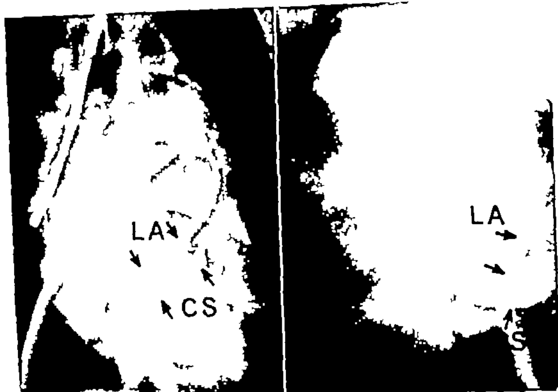


Fig. 3 Proximity of bipolar electrode catheters positioned in the coronary sinus (*CS*) and inferior left atrium (*LA*). Anterior posterior and left lateral views.

imus at greater milliamperage often resulted in ventricular stimulation. Cessation of pacing resulted immediately in a return to NSR and normal P waves in all instances.

Standard 12 lead ECG's were recorded at a paper speed of 25 mm. per second. Orthogonal leads and P loops were recorded according to the Frank system[14] on Sanborn 1507A vector system and Hewlett Packard CO4-197A oscilloscopic camera. The X, Y and Z ECG's were recorded at sweep speed of 100 mm. per second and calibrated for a 1.0 mv. per centimeter deflection. A unique feature of the vector recording system permitted the isolation and display of the P wave, so that P loops could be displayed and recorded at a sensitivity of 0.05 mv. per centimeter with selected dash-time intervals of 2.5 msec. The blunt end of the teardrop represented the leading edge. Care was taken to ground electrical equipment. The isolation and recording of P loops of high amplification and detail in the frontal, left sagittal and horizontal planes were easily accomplished except during a sinus arrhythmia. Determinations of the mean P vectors (mPv) in the three planes, frontal (F°), left sagittal (SL°) and transverse (H°)[a] were made directly from the photographic recordings of the P loops.

Unipolar right atrial electrograms (Vra) were obtained during NSR, LAR and CSR to demonstrate the sequence of atrial activation.

Studies in patients. A total of 14 patients was studied. Twelve studies were made in the course of diagnostic cardiac catheterization procedure after an informed consent had been obtained; all were in NSR with normal atrioventricular conduction. Two patients had classical electrocardiographic evidence of a spontaneous CSR. Their electrocardiograms and P loops were recorded for comparison with those obtained during paced CSR.

All patients were studied in the supine



Fig *1* Bipolar electrode catheter positioned at three locations in the coronary sinus at the os (*A*) midportion (*B*) and peripherally (*C*) in a dog Anterior-posterior views.

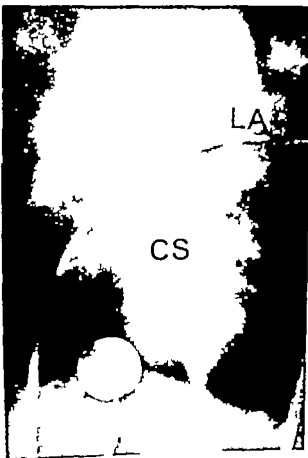


Fig. *2* B polar electrode catheter positioned in the left atrial appendage (*LA*) in a dog *CS* = Coronary sinus. Anterior posterior view

All animals were anesthetized with intra venous sodium pentobarbital A No 6 Fr bipolar or tripolar electrode catheter (elec trodes 10 mm apart) was inserted into the right external jugular vein and positioned fluoroscopically so that the distal electrode was just beyond the coronary sinus os. In addition recordings were obtained during single pacing at three locations in the great cardiac vein just beyond the coronary sinus os, at the midportion of and distally in the coronary sinus (Fig 1)

In 7 dogs a No 4 Fr bipolar electrode catheter was also positioned in the left atrial appendage by passage through a No 9 Fr Brockenbrough catheter which had been passed transseptally (Fig 2) In an additional four studies the left atrial elec trode catheter was positioned inferiorly near the great cardiac vein (Fig 3) Care was taken to minimize trauma during the transseptal procedure There was no elec trocardiographic evidence of injury before during or after single pacing of the left atrium

ECG s and P loops were recorded sequen tially during NSR and during paced CSR and LAR Single pacing at a rate just above the normal sinus rate was accomplished with a Medtronic pacemaker No 5839 which delivers impulses of 2 milliseconds duration The milliamperage was adjusted between 2 and 5 Ma to assure reliable capture and to minimize the area of elec trical stimulation Pacing the coronary

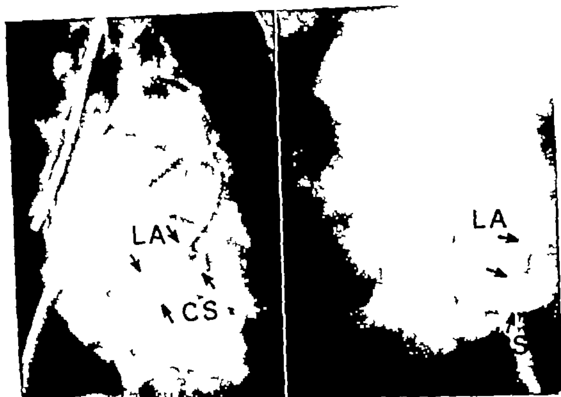


Fig. 3. Proximity of bipolar electrode catheters positioned in the coronary sinus (*CS*) and inferior left atrium (*LA*). Anterior-posterior and left lateral views.

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All patients were studied in the supine

resting position with their limbs parallel to the trunk during the recording of ECG s and P loops. Under local anesthesia a No 7 Fr bipolar electrode catheter was inserted percutaneously into an antecubital vein and positioned fluoroscopically so that the distal electrode was just beyond the coronary sinus os. Electrical pacing at a rate just above the normal sinus rate and the recording of ECG s and P loops were accomplished as described above. ECG s and P loops were recorded sequentially during NSR and during simulated CSR There were no abnormalities of ventricular activation during pacing

Three of these 12 patients had an atrial septal defect of the secundum type providing an opportunity to study simulated LAR A No 7 Fr bipolar electrode catheter was positioned in the left atrial appendage in the three patients (similar to Fig 2) and in the inferior left atrium in one of the patients (similar to Fig 3) ECG s and P loops were recorded during NSR and simulated LAR

Cessation of pacing in the left atrium or coronary sinus always resulted in an immediate conversion to normal P waves and intra-atrial electrograms

Results

A summary of the electrocardiographic P wave patterns and mean P vectors for both animal and patient studies is presented in Table I and Fig 4 Mean F° and SL are shown here since in all cases these two planes most clearly present the P vector in three directions. Although the P

Table I Summary of P wave and P loop changes

Subjects	*Rhythm*	*Mean PR (sec)*	*I*	*II*	*III*	*aVR*	*aVL*	*aVF*	V	V
Dogs 9 studies	SR	0 12	↑9	↑9	↑9	↓9	↑1 ↓7 →1	↑9	↑5 ↓ ↑2 ↑ ↓1 ↑1	↑9
8 studies	CSR	0 13	↑1 ↓6 →1	↓8	↓8	↑8	↑8	↓8	↑2 ↓4 →1	↑2 ↓4 →2
7 studies	SLAR	0 14	↑1 ↓4 →2	↑5 ↓ ↑1 ↑ ↓1	↑5 ↑ ↓2	↑1 ↓3 ↑ ↓2 →1	↑1 ↓4 →2	↑5 ↑ ↓1 ↓ ↑1	↑5 ↓2	↑6 ↓1
4 studies	ILAR	0 13	↓4	↓4	↓4	↑4	↑4	↓4	↑2 ↓2	↑2 ↓2
Patients 12 studies	SR	0 17	↑11	↑11	↑9 ↓2	↑1 ↓9	↑4 ↓3 ↓ ↑2 →1	↑11	↑3 ↓2 ↑ ↓6	↑10
14 studies	CSR	0 17	↑4 ↓8 ↓ ↑1 →1	↓14	↓14	↑12 →1	↑11 ↓1 ↓ ↑1	↓14	↑10 ↓3 ↓ ↑1	↑5 ↓4 ↓ ↑3 →1
3 studies	SLAR	0 18	↓3	↑3	↑3	↓2 ↑ ↓1	↓3	↑3	↑2 ↓1	↑1 ↓1
1 study	ILAR	0 16	↓			↑		↓	↑	

↑ = Upright P wave; ↓ = Inverted; → = Isoelectric; SR = sinus rhythm CSR = coronary sinus rhythm; SLAR = superior left atrial number of studies, incomplet electrocardiograms ere recorded

waves in the orthogonal X Y and Z ECG s provided useful data for determining their vectors in many cases, the P loops were more definitive.

Animal studies

NORMAL SINUS RHYTHM During normal sinus rhythm the P vector was directed leftward caudad and ventrad. F° was in every case in the 0 to +90 degree quadrant (range +34 to +76 degrees) In the frontal plane the F° for the group was +57 degrees. SL for the group was +113 (range +84 to 140 degrees) Typical recordings are shown in Fig 5 In all cases the P wave was upright in Leads I II III and aV$_F$ and across the precordium from V to V$_6$.

CORONARY SINUS RHYTHM Pacing the coronary sinus os produced in all animals a cephalad direction of the P loop. F° for the group was −88 (range −60 to −92 degrees) and SL was −87 degrees (range −62 to −115 degrees) In all cases the P wave was inverted in Leads II III aV$_F$ and V$_6$. In six of the eight studies the P wave was also inverted in Lead I *Four dogs showed in* addition to inverted P waves in Leads II III and aV$_F$ inverted P waves in all of the precordial leads. Typical recordings are shown in Fig 6. Pacing within the great cardiac vein was also accomplished at three locations, i.e. the os, the mid and peripheral portions. At all three locations pacing produced a similar cephalad direction of the P loop and similar scalar P-wave changes. There was no significant change in the mean P R interval during simulated CSR.

LEFT ATRIAL RHYTHM Pacing the left

F	F	V	V	X	Y	Z	Mean		Range
							F°	SL	
↑9	↑9	↑9	↑9	↑9	↑9	↑1 ↓8	+57	+113	F° +34 to +76° SL +84° to +140°
↑2 ↓5 →1	↑1 ↓5 →3	↓7 →1	↓8	↑4 →4	↓8	↑2 ↓3 →5	−82	−87	F° −60° to −92° SL −62° to −115° 4 with ↓P V to V
↑5 ↓1 ↑↓1	↑5 ↓1 ↑↓1	4 ↓2 →1	↑3 ↓2 →2	↓3 ↓↑2 →2	↑7	↑1 ↓4 →2	+113	+97	F° +94° to +131° SL +67° to +129° 3 with dome-dart in V 1 with ↓P V to V
↑1 ↓3	↑1 ↓3	↓4	↓4	↑1 →3	↓4	↓1 →3	−80	−104	F° +60° to +89° SL +90° to +120° 2 with ↓P V to V
↑10	↑10	↑10	↑11	↑10 →1	↑10 →1	↑1 ↓↑3 →7	+52	+101	F° +22° to +78° SL +80° to +136
↑2 ↓7 ↓↑3 →1	↑1 ↓9 ↓↑2 →1	↑2 ↓9 ↓2	↓12 ↓↑1 →1	↑3 ↓8 →1	↓12	↑1 ↓1 →10	−88	−87	F° −50° to −110° SL −61 to −103° 2 with ↓P V to V 1 with "dome-dart" in V 2 spontaneous CSR
↑1 ↓1	↑1 ↓1	→2	↑1 ↓	↓2	↑2	↓1 →1	+109	+123	F° +107° +115° SL +122° +123° 1 with "dome-dart in V Dome-dart in V

rhythm, ILAR inferior left atrial rhythm. Numbers after arrows denote number of occurrences, where the sum did not equal the

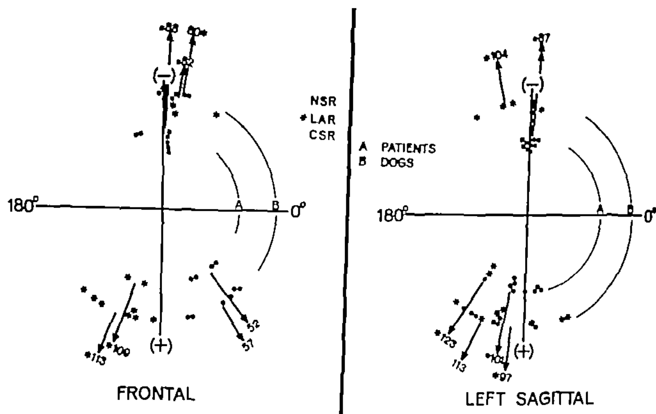


Fig 4 Summary of mean P vectors during sinus rhythm (VSR) simulated left atrial (*LAR*) and coronary sinus (*CSR*) rhythms in the frontal and left sagittal planes. Positive F° and SL during LAR were obtained during pacing of the left atrial appendage negative F° and SL during pacing of the inferior left atrium.

atrial appendage of seven dogs produced a group F° of +113 degrees (range +94 to +134 degrees) and SL of +97 degrees (range +67 to 129 degrees) The mean P R interval during simulated LAR was 20 msec longer than the control mean value Five of 7 animals had upright P waves in II III and aV$_F$ Three of the animals demonstrated a dome-dart configuration of the P waves in V$_1$ Three showed inverted P waves in Leads V$_1$ to V$_4$ Typical recordings are shown in Fig 7 As indicated in Table I the P wave changes were variable and nonspecific often biphasic and of low voltage in almost any lead Since it is conceivable that there are other areas from which left atrial rhythm might originate the term superior left atrial rhythm is used because the P loop is directed caudad

Stimulation of the inferior wall of the left atrium in four dogs, near the great cardiac vein produced P loops and scalar P wave changes which were indistinguishable from simulated CSR Typical electrocardiograms and P loops are shown in Fig 8

INTRA ATRIAL CONDUCTION Typical recordings of Vra during NSR and during paced inferior LAR and CSR are shown in Fig 9 The right atrial potentials during simulated inferior LAR and CSR are identical and the polarity is similarly reversed from those of NSR

Further confirmatory data to show reversal of the sequence of atrial activation during LAR was obtained by positioning a bipolar electrode catheter in the right atrial appendage at its junction with the superior vena cava for the recording of Bachman bundle (BB) potential The configuration of the BB potential conforms with the characteristics described by Wagner and coworkers.[14] During left atrial stimulation the polarity of the BB potential was reversed from that recorded during sinus rhythm (Fig 10) indicating a reversal in the sequence of interatrial conduction.

Patient studies

NORMAL SINUS RHYTHM F° for this group of 12 patients was +52 degrees (range 22 to 78 degrees) and +101 (range +80 to +136 degrees) in the left sagittal plane. The leftward caudad and ventrad direction of the P loop in patients wa to

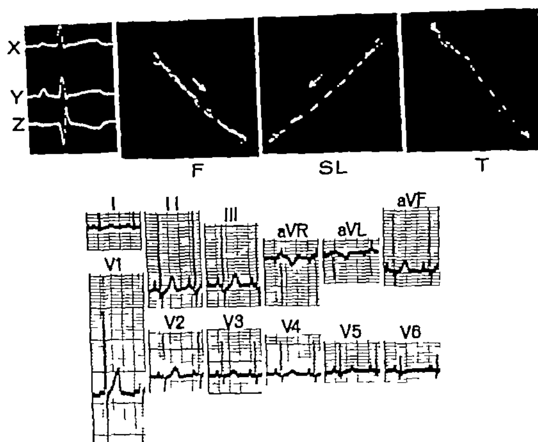


Fig. 5 Orthogonal (X, Y and Z) ECG (paper speed 100 mm. per second) P loops in the frontal (*F*) left sagittal (*SL*) and transverse (*T*) planes, and 12 lead ECG during *normal sinus rhythm* in dog. The blunt end of the dash-time lines (2.5 msec. intervals) represent the leading edge. In the transverse plane the upper half is dorsal, the lower half ventrad, as viewed from above.

that in animals. Typical recordings are shown in Fig. 11.

CORONARY SINUS RHYTHM. Pacing just within the coronary sinus os produced findings similar to those of the animals studied (Fig. 12). In all cases the P loops were directed cephalad. F° was −82 (range −50 to −110 degrees) and SL −87 (range −61 to −113 degrees). The P waves were always inverted in Leads II, III, and aV_F. In 12 of the 14 studies the P wave was also inverted in V_1; in two the P waves were isoelectric. In only one patient was dome-dart P waves in V_1 observed (Fig. 13). The P-R interval during coronary sinus pacing was unchanged from control values.

LEFT ATRIAL RHYTHM. P loops were recorded in two of three patients in whom the left atrial appendage was paced; the P loops had a rightward, caudad, and ventrad direction (Fig. 14). The P waves were inverted in Lead I and upright in Leads II, III, and aV_F. F° was 102 and +115 degrees and SL +122 and +123 degrees, respectively; the mean P vectors in the frontal and left sagittal planes were in the same quadrants as those in the animals with simulated LAR of the same focus. In these three cases the P waves were upright in V_1, and one patient demonstrated the "dome-dart" configuration of the P wave. In one patient in whom the inferior left atrium was paced, the P wave was inverted in Leads I, aV_F, and V_6, and upright in aV_R and V. The P wave in V had a dome-dart configuration.

Discussion

In the present investigation, the production of coronary sinus and left atrial rhythms did not require an extensive surgical procedure. The normal configuration

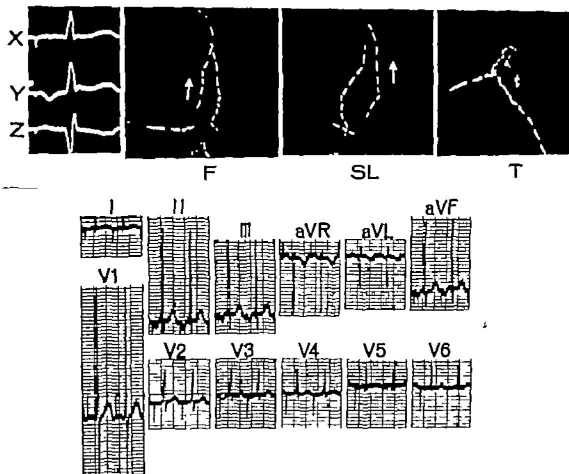


Fig 6 Same dog as in Fig 5 during simulated *coronary sinus rhythm* The P waves are inverted in Y Leads II III and aV_F upright in aV_R and isoelectric in V to V_6. The P loop is cephalad.

magnitude and direction of the P waves prior to and immediately following cessation of pacing indicate that the procedures employed did not cause any significant anatomic alteration of the atrial conduction pathways which might account for the changes noted

In 1965 Lancaster and co-workers[3] reported that the clinical criteria for a coronary sinus rhythm could be experimentally reproduced in man These investigators using an electrode catheter paced the os of the coronary sinus of 8 patients and produced inverted P waves in Leads II III and aV_F The P vector during pacing was directed superiorly to the right and anteriorly In only one patient was the P loop directed posteriorly The results of the present study are in agreement with their findings.

On the other hand our findings are in disagreement with those of Moore and co-workers[4] who used a different technique to investigate the polarity of the P wave during simulated coronary sinus rhythm These investigators used surface bipolar electrodes chronically implanted in the region of the coronary sinus of dogs the os was not entered They reported that driving the atria from the coronary sinus region produced essentially no change in the P vector in all dogs except two These latter animals did demonstrate reversed polarity of the P vectors which were attributed to intra atrial conduction defects produced by thrombus formation and other anatomic lesions occurring secondary to surgical manipulation Similarly Massumi and co-workers[11] found variability in the P waves when the region of the coronary sinus of 7 patients was paced using an electrode catheter It is to be noted that these investigators diligently avoided the interior of the coronary sinus during the pacing procedure.

Thus it would appear that one of the

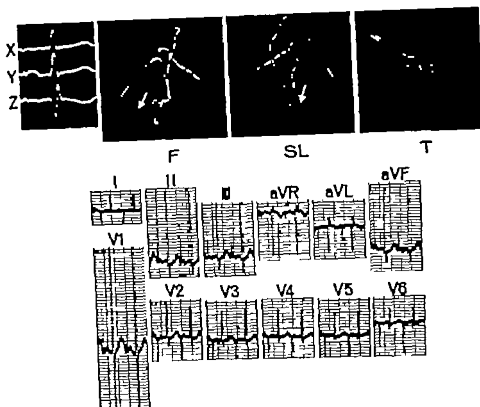


Fig. 7. Same dog as in Figs. 5 and 6, during stimulation of the left atrial appendage (*superior left atrial rhythm*). The P loop is directed rightward, caudad, and anterior. The P wave is isoelectric in Lead I, biphasic in II, III, and V, upright ("dome-dart") in V and inverted in V and V_6.

major reasons accounting for the apparent discrepancies in the results reported by Moore and co-workers and Massumi and co-workers with those reported by Lancaster and co-workers and us resides in the investigators' methods applied. In the two former studies the "region of the coronary sinus" was electrically stimulated, while in the latter two studies the os of coronary sinus was entered and stimulated. Therefore it would appear that there is no need to invoke local disturbances in conduction and P-wave aberration to account for the reported differences. Finally, our results show that the diagnostic criteria for a coronary sinus rhythm are satisfied even when various regions of the great cardiac vein of dogs are electrically stimulated.

Another consistent finding in all of our coronary sinus pacing studies in dogs and also in a majority of human studies was the production of an inverted P wave in V_6. Mirowski[1,19] has recently contributed several articles bearing on the clinical criteria of left atrial rhythms. He stated that left atrial pacemakers may be located anteriorly or posteriorly and that the most sensitive and specific sign of left atrial rhythms appears to be the inverted P wave in Lead V_6. Mirowski has also described similar clinical tracings which he states were erroneously diagnosed as coronary sinus or nodal rhythms, but which he attributes to being ectopic rhythms originating anteriorly in the left atrium.[19] In our coronary sinus pacing studies 4 dogs and 2 patients demonstrated, in addition to inverted P waves in Leads II, III, and aV, inversion of the P waves in all of the precordial leads; these changes cannot be attributed to an anterior left atrial focus. Our results further indicate that inversion of the P wave in Lead V is common to both CSR and inferior LAR.

Pacing the left atrium in the region of the appendage produced less consistent fin-

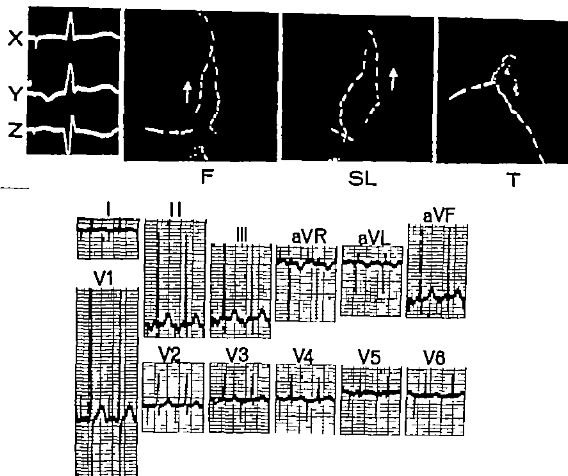


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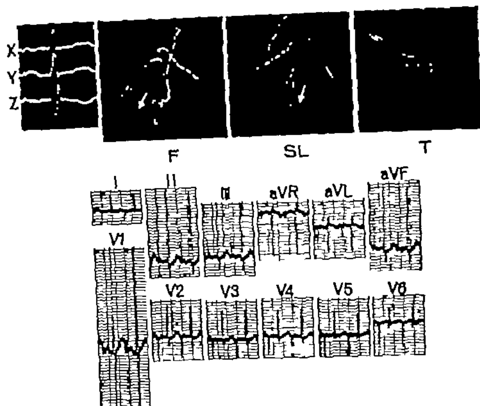


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Pacing the left atrium in the region of the appendage produced less consistent findings

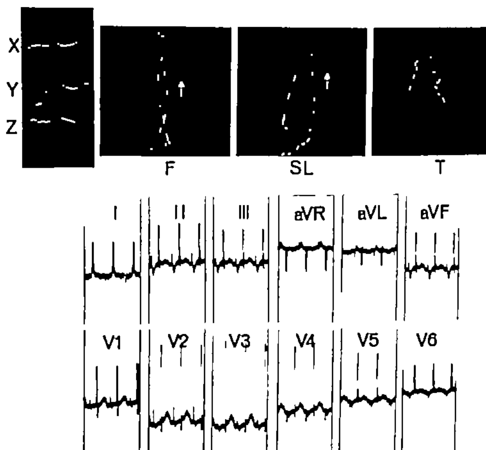


Fig 8 Simulated *inferior left atrial rhythm* The P waves and P loops are identical with those during coronary sinus rhythm (Fig 6) In addition, the P waves are inverted in V through V_6.

than the results of coronary sinus pacing While the P loops in every case were directed rightward and caudad in the frontal plane (i e. >90 degrees) inversion of the P waves in Leads I and V_6 was not always obtained The varied and nonspecific P wave changes may be due to strategic electrocardiographic lead location relative to the vectorial presentation of intra-atrial conduction In 3 of 7 animal studies and in 2 of 4 human studies a dome-dart configuration of the P wave appeared in V_1 This variant of a left atrial rhythm has been previously described as originating from a posteriorly located left atrial focus[9] and was a rare finding in our coronary sinus pacing studies.

Recently Harris and co-workers[12] studied the left atrial P wave and loop in 11 patients in whom various regions of the left atrium was paced They found that the P wave configuration in Leads I and V_6 were highly variable and concluded that reversal of the sequence and direction of activation of the P wave in Lead V_1 was most important in the diagnosis of LAR

A recent report[13] indicated the inadequacy of diagnosing ectopic supraventricular rhythms by electrocardiographic analysis when the criteria proposed by Mirowski are applied in all of this study s cases the P loop was different from that postulated by the scalar electrocardiogram The results of our investigation also indicate the additional usefulness of obtaining P loops for the differentiation of supraventricular ectopic rhythms.

If the focus is located inferiorly in the left atrium or in the coronary sinus the P vector is directed cephalad The consistency of our findings suggest that atrial rhythms arising from within the coronary sinus os may in fact be of inferior left atrial origin Others[4,17,18] have previously suggested that this may be the case since the coronary sinus is embryologically a left atrial structure Although additional investigations in this area are required further support for this contention is offered in Figs. 3 and 10 Fig 3 depicts the

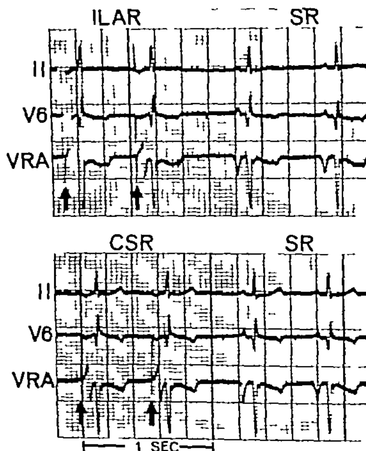


Fig. 9 Leads II, V and Vra during sinus rhythm, and paced coronary sinus and inferior left atrial rhythms. The P waves are identical in configuration and polarity during the latter two rhythms. The arrows indicate the pacer impulse artifact.

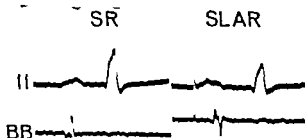


Fig. 10 Lead II and Bachman bundle potential (BB) during sinus rhythm (SR) and during superior left trial rhythm (SLAR). The polarity of the BB potential is reversed during SLAR. The sequence of trial activation is also reversed as indicated by the change in P-wave configuration in Lead II

Fig. 11. Orthogonal ECG, P loops, and 12 lead ECG in a patient with an atrial septal defect during *normal sinus rhythm.*

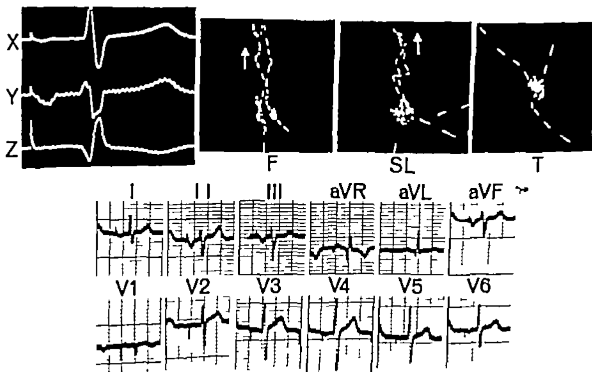


Fig. 12. Paced coronary sinus rhythm in a patient. The P waves are inverted in Y. Lead I, II, III, aV_F and V_4 to V_6, and upright in aV_R. The P loop is directed cephalad (cf., Figs. 6 and 8).

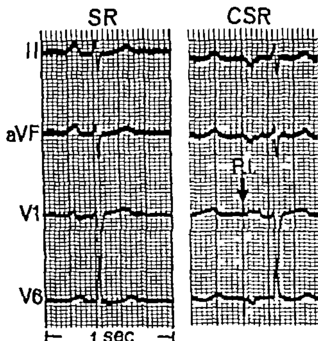


Fig. 13 "Dome-dart" P wave in V during paced *coronary sinus* rhythm in patient. *SR* = Sinus rhythm; *CSR* = coronary sinus rhythm.

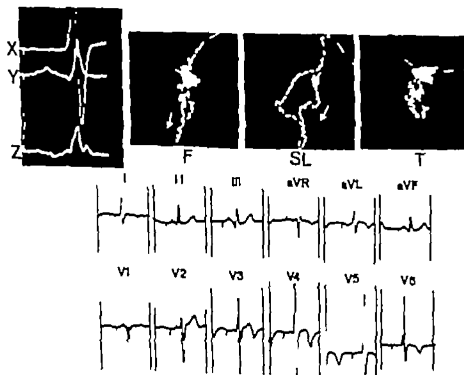


Fig. 14 Same patient as in Fig. 11 during paced *superior left atrial* rhythm (cf Fig. 7)

Fig *11* Orthogonal ECG P loops and 12-lead ECG in a patient with an atrial septal defect during ***normal sinus rhythm***

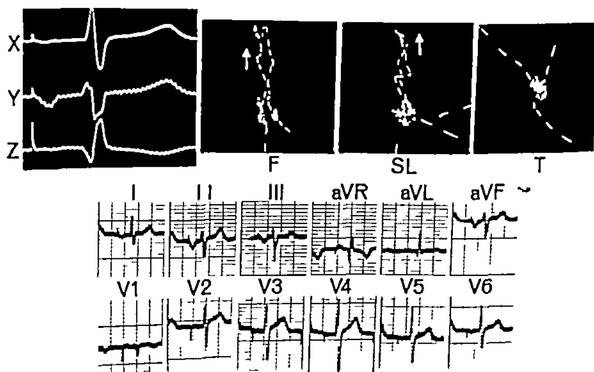


Fig *12* Paced coronary sinus rhythm in a patient. The P waves are inverted in Y Leads I II III aV_F and V_4 to V_6 and upright in aV_R. The P loop is directed cephalad (cf., Figs. 6 and 8)

The use of the digital computer in the study of patients during exercise-induced stress

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Exercise stress testing of various types plays an important part in the evaluation of patients with cardiorespiratory complaints. Traditionally, observation of heart rate, blood pressure, the electrocardiogram, and clinical symptomatology has been made during exercise of various types and intensity. Efforts have been made by Masters,[1,2] Bruce and associates,[3] and others to standardize the exercise work load, to describe normal and abnormal responses to exercise, the significance of the abnormal responses, and just what parameters to measure during exercise.

Recent interest has centered around changes in the electrocardiogram during and after exercise.[4,5] Recording of an electrocardiogram during active exercise poses difficult problems with artifacts that are not completely resolved by lead and electrode placement, skin preparation, or radio transmission of the electrocardiogram (ECG). A method of providing an artifact-free yet accurate ECG is greatly needed. Computer analysis techniques appear to provide a reasonable solution to this problem.

Ventilatory gas analysis at rest and during exercise provides additional information regarding the functional capacity of a subject's cardiovascular-respiratory system. The relationships between work rate and oxidative energy have been studied in normal subjects by Wasserman and associates.[6] Maximum oxygen uptake is a measure of the total oxygen transport capacity of the cardiovascular respiratory system and thus is an index of the relative degree of cardiovascular fitness. Holmgren[7] has recently reviewed data regarding the relationships between various functional capacities and dimensional factors which determine maximum oxygen uptake. These dimensional factors such as oxygen uptake, carbon dioxide production, respiratory quotient (RQ), minute volume, and tidal volume can now be measured breath by breath and when done so during quantitated progressive exercise truly reflect an individual's functional capacity.[8] Braunwald[9] found that digitalization of patients with mild congestive heart failure lowered the oxygen debt accumulated during treadmill exercise.

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proximity of electrode catheters fluoroscopically placed within the coronary sinus and in the inferior left atrium Thus an electrical impulse delivered through either catheter may excite contiguous atrial tissue or utilize a common intra atrial conduction pathway with the resultant P wave configurations P loops, and intra-atrial electrograms being identical and indistinguishable From our data it would appear that the P wave configuration and polarity are dependent not only on the site of impulse formation but also on the conduction pathways utilized

Summary

P wave and P loop changes during transvenous pacing of specific locations in the coronary sinus and left atrium were studied in dogs and in man

During coronary sinus rhythm the diagnostic criteria for P wave changes were always met. In addition inversion of the P wave in Lead V_6 was consistently obtained The P loop was always directed cephalad Dome-dart P waves in V_1 were present in one of 14 patient studies

Pacing the left atrial appendage produced less consistent P wave changes dome dart P waves in V_1 were present in 3 of 7 dog studies and in one of 3 patients The P vector was directed caudad rightward and ventrad

Pacing the inferior left atrium in close proximity to the coronary sinus produced P wave and P loop changes which were identical with and indistinguishable from those of coronary sinus rhythm It is suggested that a common site of impulse formation or a common intra-atrial conduction pathway is utilized

Confirmatory evidence was obtained from intra atrial electrograms. Additional evidence was obtained from Bachman bundle potential recordings which indicated a reversal of atrial activation during left atrial rhythm

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graph is measured with a transducer (Statham PM5TC-0.15 PSI) energized (Hewlett Packard No 8016) and amplified (Dana 3400VI) to provide to the computer a voltage level of 2 volts per centimeter of water pressure applied to the transducer In series with each tube (3/16 in., inner diameter) that connects the pneumotachograph to the transducer are three-way valves (Skinner Valves, New Britain, Conn) under computer control which switch the transducer to room air pressure to establish zero flow voltage.

The gas sample from the subject is measured with analyzers for CO_2 concentration (Beckman LB-1) and O partial pressure (Westinghouse, Pittsburgh Pa) with modifications[14] the 90 per cent response time of the analyzers being 0.2 (CO_2) and 0 1 (O) seconds. The low impedance output of the CO meter was coupled to an operational amplifier to provide computer voltage levels of zero volts for room air and 5 volts for 10 per cent CO_2. The O_2 meter was amplified (Dana 3400VI) and base-line controls provide computer voltage levels of −2.5 volts for room air and 4 volts for 100 per cent O_2. ECG signals were R.C. coupled to an amplifier (Dana 3400VI) with a gain of 1,000 to provide computer voltage levels of 1 volt per 1 millivolt of ECG signal.

The pneumotachograph has two modifications. First, needle tubing was soldered in place to collect gas samples from the center of the respiratory air flow Second the heating element of the pneumotachograph which reduces the problem of condensation in the resistive element, was temperature-regulated at 37° C. Thermocouple wire was cemented to the bobbin of the heater wire and coupled to a time proportional temperature controller (A.P I Model 603-K) and current to the heater coupled through the controller relay

Air flow is an instantaneous measurement but gas concentrations lag in real time because of the time required for the sample to traverse from subject to analyzers. This delay is easily measured with the C.R.O in the exercise room and is maintained at a fixed value by adjusting the sampling rate to each analyzer prior to a study The delay value is communicated to the computer for use in the calculations.

A multiposition switch in the exercise room has preassigned instructions for the computer Depression of a process-interrupt button informs the computer to sense what position the switch is in and follows the assignment of that position The assignments are as follows (1) Standard gas (computer stores voltage levels for room air CO and O_2 concentration) 2 Calibration gas (computer stores voltage levels for CO_2 and O_2 concentrations of calibration gas determined by Scholander analysis) (3) start of study (4) mark (provides a marker on the permanent record at points of interest such as start of exercise) (5) end of study

Voltage levels for zero air flow are automatically sensed by computer controlled valves, and used for computation prior to every 30 second analysis.

One of two treadmill tests is *currently* being used. Most often the Bruce[3] test is used beginning with a work load of 1 7 M.P.H at 10° incline increasing automatically both speed and incline at three minute intervals. *On* occasion a modification of the first test is selected for patients with severe functional incapacity The modified test begins with a workload of 1 m.p.h at a 10 degree incline with alternate increases of 0.5 m p.h. and 2 degree grade at three minute intervals. The selection of which test to use is made by the physician conducting the test.

The subject is prepared for the study by a technician who calibrates and operates the apparatus. Each study is supervised by the physician. A wall chart lists several statements such as yes no chest pain, short of breath stop etc., and allows the subject a means of communicating with the people conducting the test.

The exercise room is strategically located in the main heart station of the medical center where cardiologists are available should an emergency arise. A defibrillator drugs, and oxygen are placed in the room, should they be needed.

An artificial lung consisting of a double syringe and valve arrangement, designed to pass known volumes of gases of known composition through the system was used to derive errors in the respiratory gas computation. With respiratory rates of 6 per minute errors were oxygen volume



Fig 1 Subject connected to pneumotachograph assembly with ECG electrodes in place.



Fig 2 Exercise room apparatus.

Traditionally ventilatory gas analysis has been done by collecting in bags all air expired over a minute or more of a steady state either rest or exercise. The collected air has then been measured for volume and concentration of gases under study thus arriving at average values of oxygen consumption carbon dioxide production and RQ during the time under study This method is somewhat cumbersome and is of limited value when studying the transients between rest and steady-state exercise Individuals with impairment of cardiac function are frequently unable to achieve a steady state even during low work loads of exercise. Since our laboratory is primarily involved in the study of cardiac patients we have endeavored to evolve a system with which to study individuals with all degrees of functional impairment. The purpose of this report is to describe such a system of electrocardiographic and ventilatory gas analysis.

Methods and materials

As shown in Fig 1 the subject breathes through a pneumotachograph (Instrument Assoc New York) with modifications and mouth piece (Warren Collins) assembly supported by a leather strap from a rod assembly riveted to a French bicyclist helmet The resistance element of the pneumotachograph produces a differential pressure (± 1 cm of H_2O) proportional to the rate of flow A continuous respiratory gas sample (2 L. per minute) is drawn distal to the subject and pneumotachograph ECGs are sensed from adherent patient electrodes (Electronics for Medicine White Plains N Y)

Fig 2 shows the apparatus located in the exercise room Subjects are exercised on either a treadmill (Quinton Instrument Co Model 1860 Seattle Wash) or a bicycle ergometer (Monarch Sweden) A cabinet houses the gas analyzers transducer controls, amplifiers and an oscilloscope (C R O) for monitoring the four primary analogue signals. Signals monitored are air flow per cent of carbon dioxide partial pressure of oxygen (referenced to room air) and ECG A television set displays the computer-generated data

The differential pressure proportional to the rate of flow through the pneumotacho-

graph is measured with a transducer (Statham PM5TC-0 15 PSI) energized (Hewlett Packard No. 8016) and amplified (Dana 3400VI) to provide to the computer a voltage level of 2 volts per centimeter of water pressure applied to the transducer. In series with each tube (3/16 in., inner diameter) that connects the pneumotachograph to the transducer are three-way valves (Skinner Valves, New Britain, Conn.) under computer control which switch the transducer to room air pressure to establish zero flow voltage.

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(VO_2) -2 to $+1.2$ per cent carbon dioxide volume (VCO_2) -0.9 to 1.8 per cent tidal volume (V_T) -0.8 to -4.1 per cent at rates of 12 per minute VO_2 -0.4 to -2.2 per cent VCO_2 -0.6 to -1.7 per cent V_T -3.3 to 2.3 per cent at rates of 24 per minute VO_2 -2 to $+1.2$ per cent. VCO_2 -0.9 to -1.9 per cent and V_T -0.1 to $+0.5$ per cent. Should the value of lag between the flow and gas signals be set so that gas concentration leads flow in real time the computation will indicate greater gas transfer than actually occurred Should the lag be the opposite the computed value is smaller than actually occurred The syringe system is used daily to calibrate the apparatus.

Keyboard entries of gas and flow calibration coefficients and lag between flow and gas signals are made at the computer

Data acquisition and analysis An IBM 1800 digital computer passes the four primary signals through an analogue to digital converter at approximately 250 samples per second From these basic parameters others are calculated and displayed These other parameters are also logged on an IBM 2310 3 disc storage unit and are available for processing directly from the disc for a period of up to three days. The length of time the data are stored is inversely proportional to the total monitoring activity of the system

Two events considerably eased the problem of processing displaying and recording the exercise data one an extensive patient monitoring system described by Osborn and associates[11] using the computer complex had been developed tested and in use for many months and two the respiratory sensing apparatus used in the exercise room had served as a prototype for the respiratory portion of the patient monitoring system Thus the algorithms for measuring respiratory parameters were already available reliable and in use.

The approach used during the study was to collect respiratory measurements for a period of 30 seconds and ECG measurements for 10 seconds. The data collected and analyzed is then displayed on a television screen in the exercise room and also saved in a mass storage device for later

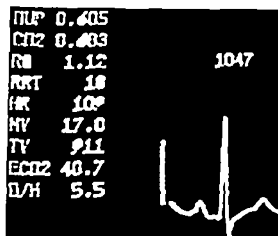


Fig 3 Television display in the exercise room.

processing This process is repeated in all following 40 second intervals until the study is completed Fig 3 shows the parameters that are displayed on the television screen in the exercise room They are as follows time of analysis oxygen uptake (OUP) carbon dioxide production (CO_2) respiratory quotient (RQ) respiratory rate (RRT) heart rate (HR) minute volume (MV) tidal volume (TV) end-expired CO_2 (ECO2) oxygen pulse (O/H) and the computer averaged ECG wave form Identifying symbols are shown in parentheses.

The method used to calculate carbon dioxide production and oxygen uptake may be of special interest. Carbon dioxide production for each breath is computed from the product of the integral of expired flow and the per cent of carbon dioxide. The carbon dioxide production for the 30 second sample period is then extrapolated to yield carbon dioxide production for a full minute Breath by breath inspired and expired oxygen is calculated in a similar manner The difference between the inspired and expired oxygen for the 30 seconds is again extrapolated to give oxygen uptake for one minute.

A continual check on the reliability of part of the system is made using the tidal volume. Flow is integrated during inspiration and expiration for tidal volume measurements. If these volumes differ by more than 10 per cent the logged information is noted providing an indicator of possible apparatus malfunction

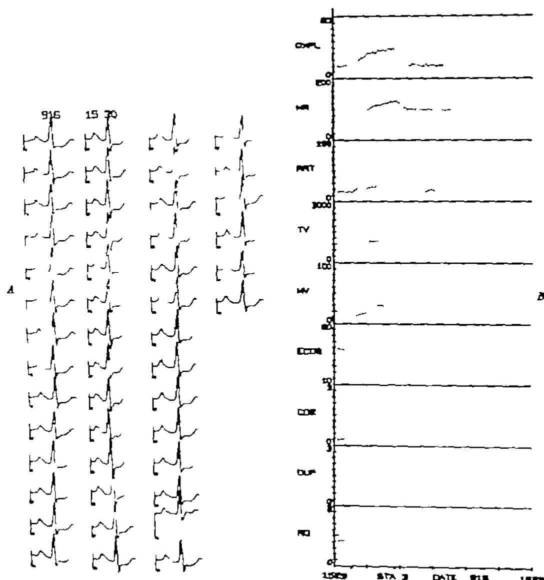


Fig 4 Permanent record of respiratory data and ECG wave forms. *A* Averaged ECG wave forms at 40 second intervals. *B* Some of the available linear plots. Ten minute intervals marked on lower horizontal axis. Start and stop of exercise marked by arrows. Parameters plotted from top to bottom are *OXPL*, oxygen pulse; *HR*, heart rate; *RRT* respiratory rate; *TV* tidal volume (milliliters); *MV*, respiratory minute volume (liters); *ECO2*, end-expiratory P_{CO_2}; CO2, CO_2 output as minute volume (liters); *OUP* oxygen uptake as minute volume (liters); *RQ* respiratory quotient.

During the approximately 10 seconds that ECG data are being collected 2 400 analogue-to-digital conversions are made. Using this information and centering on each R peak, the ECG's are averaged and displayed on the television screen as a single ECG. This technique has resulted in smooth curves that compare well with simultaneous strip chart records.

It is felt that the ECG 10 second sampling period is short enough so that heart rate changes will ordinarily not affect the averaging technique. However the problem of ectopic beats does arise. Ectopic beats occur most frequently at rest and rarely during strenuous exercise. Those seen at rest virtually always disappear when exercise is started. Those ectopic beats that occur during higher work loads of exercise are easily recognized on the oscilloscope

(VO_2) −2 to + 1 2 per cent carbon dioxide volume (VCO_2) −0 9 to 1 8 per cent tidal volume (V_T −0 8 to −4 1 per cent at rates of 12 per minute VO_2 −0 4 to −2 2 per cent VCO_2 −0 6 to −1 7 per cent V_T −3 3 to 2 3 per cent at rates of 24 per minute VO_2 −2 to + 1.2 per cent. VCO_2 −0 9 to −1 9 per cent and V_T −0 1 to + 0 5 per cent. Should the value of lag between the flow and gas signals be set so that gas concentration leads flow in real time the computation will indicate greater gas transfer than actually occurred Should the lag be the opposite the computed value is smaller than actually occurred The syringe system is used daily to calibrate the apparatus.

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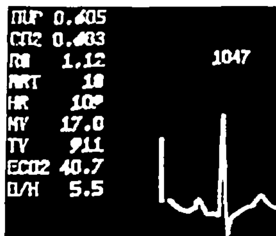


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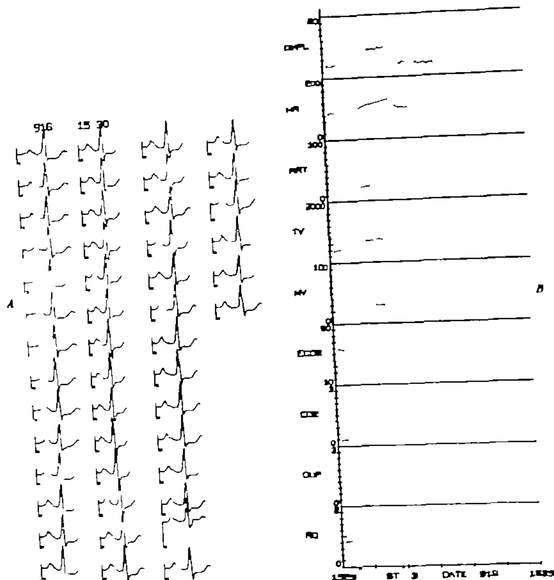


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During the approximately 10 seconds that ECG data are being collected, 2,400 analogue-to-digital conversions are made. Using this information and centering on each R peak, the ECG's are averaged and displayed on the television screen as a single ECG. This technique has resulted in smooth curves that compare well with simultaneous strip chart records.

It is felt that the ECG 10 second sampling period is short enough so that heart rate changes will ordinarily not affect the averaging technique. However, the problem of ectopic beats does arise. Ectopic beats occur most frequently at rest and rarely during strenuous exercise. Those seen at rest virtually always disappear when exercise is started. Those ectopic beats that occur during higher work loads of exercise are easily recognized on the oscilloscope

and usually call for termination of exercise.

After the procedure processing the ECG data presented a problem because of system storage constraints Displaying the average of an ECG at our sampling rates can take upward of 250 points. The exercise procedure takes as long as 50 minutes It was felt that in our particular system this represented too much information to be logged The problem then was to see if we could validly represent an averaged ECG with fewer points. It turned out that by taking the mean of each 4 points of the already averaged ECG of 2 400 points and saving this information we can reconstruct the original ECG in an accurate manner at a later date

The processing of the data acquired in the exercise lab is completed the following morning At that time the information stored on the disc is retrieved plotted and printed Graphs are made with a Calcomp plotter connected to the IBM 1800 An example of the plotted output is shown in Fig 4 Also a numerical chart is made on an IBM 1443 line printer

Alternate analogue computations Osborn and associates[12] have reported preliminary respiratory studies using a prototype of the gas-sensing apparatus described with computations made with an analogue computer Primary signals of gas concentration and air flow were recorded on magnetic tape (Ampex Sp300) Flow was delayed by recording the signal during the study and synchronizing was achieved by adjusting the rate of gas sampling At a later time the recorded tapes were replayed into an analogue computer (EAI TR20) and were recorded (Electronics for Medicine DR 8) and permanent records measured and plotted

The time required to process the records (2 to 3 days) did not provide the physician with indicators of immediate patient condition however analogue computation can be used to advantage when digital computers are not available.

Patient data

Two case histories are given in some detail to illustrate the value of exercise-stress testing to determine the functional capacity of the cardiovascular respiratory systems.

Case report, Patient J W J W a 58-year-old Caucasian woman, had known of a heart murmur since 17 years of age when she had had rheumatic fever Asymptomatic until the past year she now noted increasing fatigue and severe dyspnea with modest exertion. Hemoptysis and troublesome palpitations occurred prior to admission. Physical examination revealed blood pressure 100/60 pulse 72 and regular and neck veins very slightly distended. The chest was clear The cardiac impulse was in the fourth left intercostal space in the midclavicular line. A modest right ventricular lift was noticeable. The first heart sound was very loud. The second heart sound was not accentuated and split normally A loud opening snap was clearly heard along the left sternal border A Grade II/VI long diastolic rumble with presystolic accentuation was heard at the apex. Systole was clear The peripheral arterial pulses were within normal limits. No edema or hepatomegaly was present. Chest x-rays revealed definite left atrial enlargement and moderate right ventricular prominence. The pulmonary artery segment was prominent and pulmonary arterial congestion was present, especially in the upper lobes. Kerley's lines were seen at both lung bases. There were no demonstrable pleural effusions.

The electrocardiogram showed normal sinus rhythm, a QRS frontal plane axis of +80 degrees, notched P waves in Leads I aV$_L$, V$_4$, and V$_6$ and slightly negative P waves in V$_1$, compatible with left atrial enlargement. In Lead V the R.S ratio was one suggesting some right ventricular hypertrophy

At cardiac catheterization all right heart pressures were moderately elevated. Pulmonary artery wedge pressure was 22 mm. Hg and during low-load exercise rose to 32 mm. Hg Cardiac output was normal at rest and increased normally during exercise. Pulmonary resistances were within normal limits. The calculated mitral valve area was 1.85 sq cm.

Case report Patient D C D C a 46-year-old Caucasian man had rheumatic fever at the age of 6 At age 26 he had several episodes of hemoptysis associated with dyspnea on exertion. At age 31 he had a closed mitral commissurotomy with good symptomatic relief At 43 years of age severe hemoptysis recurred. Approximately 6 months previous to this evaluation the patient developed intermittent pedal edema which responded poorly to diuretics. Two months prior to admission he noted moderate dyspnea after climbing one to two flights of steps and a marked increase in the pedal edema. There was no orthopnea or paroxysmal nocturnal dyspnea. He continued to work full time as a bellboy carrying heavy suitcases in a large hotel in downtown San Francisco.

At physical examination, this patient's blood pressure was 120/80 and his pulse 80 and irregular Mild neck vein distension with a prominent "V" wave was seen with the patient at 30 degrees from the horizontal. The chest was clear except for fine inspiratory râles at the right base. The cardiac apical impulse was felt at the fifth intercostal space 2 cm lateral to the midclavicular line and a prominent right ventricular lift was felt. The first heart sound was accentuated and was followed by a Grade II/IV

high-pitched holosystolic murmur at the lower left sternal border which increased with inspiration. The second heart sound was prominent with a loud pulmonic component. A loud opening snap at the apex initiated a Grade I/VI diastolic rumble. The liver was markedly enlarged and the spleen tip was palpable. He also had 4+ pitting pedal edema which extended to the midthigh.

Chest x-rays revealed a moderately enlarged heart with prominent left atrium and right heart chambers. Marked pulmonary vascular congestion was present along with small bilateral pleural effusions. The electrocardiogram revealed atrial fibrillation with a ventricular response of 70; the frontal plane QRS axis was 95 degrees. Prominent deep S waves from V through V were considered consistent with right ventricular hypertrophy.

Cardiac catheterization revealed markedly increased right heart pressures with pulmonary artery pressure being near systemic arterial pressures. Pulmonary artery wedge pressure was 32 at rest. Cardiac output was extremely low and did not rise significantly with exercise. Both total pulmonary resistance and pulmonary vascular resistance were very severely elevated. Left ventricular end-diastolic pressure was within normal limits. During exercise the A-V systemic arteriovenous difference widened from 8.6 to 12.1 vol. per cent.

These two patients with mitral stenosis represent the two extremes of the spectrum of this disease and they demonstrate the frequently occurring clinical problem of differentiating by history patients with mild from those with severe mitral valve obstruction. Both of these patients were similarly symptomatic, yet one had mild mitral stenosis and the other had severe mitral stenosis with pulmonary hypertension and right ventricular failure.

Treadmill exercise with ventilatory gas analysis as described demonstrated clearly the distinct differences between these two patients in response to exercise. Although oxygen consumption and respiratory flow rates were similar at rest in the two patients, oxygen transport at the pulmonary level was impaired even at rest in Patient D. C. Clear evidence for this was that his ventilatory equivalent (minute volume divided by minute oxygen uptake) was consistently 40 per cent above that of Patient J. W. Circulatory transport of oxygen was also severely impaired in Patient D. C. His anaerobic threshold (point at which respiratory quotient rose consistently over 1.0) was reached at an oxygen consumption of only 521 L. per minute compared with 935 L. per minute in Patient J. W. The maximum oxygen consumption achieved by D. C. was 733 L. per minute contrasting with 1,202 L. per minute for J. W.

Discussion

ECG and ventilatory gas analyses during progressive treadmill exercise can readily differentiate between patients with varying degrees of impairment of oxygen transport. Greater pulse rate increases at a given work load are usually seen in more limited individuals, reflecting their inability to maintain or increase cardiac stroke volume as a means of increasing *cardiac output*. When over all oxygen transport is limited due to cardiovascular functional impairment, a greater portion of the oxidative energy of the body must be supplied through anaerobic metabolic pathways. This is seen as a low maximum oxygen consumption and a steadily rising RQ giving an anaerobic threshold at a low oxygen consumption and a low work rate. The relationship between minute volume and actual oxygen consumed per minute describes the efficiency of the *individual's* gas exchange.

Cardiac catheterization has been the traditionally accepted method of cardiovascular evaluation. It must remain the definitive means of accomplishing anatomic-angiographic studies. There are frequent situations when it is desirable to define an individual's over-all cardiorespiratory function without the need for specific hemodynamic and anatomic information. Such instances include the postoperative evaluation of individuals who have undergone cardiac surgery, the study of the effects of drug therapy on an individual's cardiorespiratory functional status and the long term follow up of individuals before cardiovascular surgery to determine the appropriate time for surgical intervention. A distinct advantage of this procedure is that it can almost always be done as an outpatient procedure requiring very little time, inconvenience, or patient discomfort, and it has negligible risk of mortality and morbidity.

Summary

A computer analysis technique of monitoring and measuring an individual's cardiovascular and respiratory responses to

exercise has been described in detail The proper use of this procedure yields significant data reflecting the hemodynamic status of subjects with various degrees of cardiovascular and respiratory impairment

The authors gratefully acknowledge the engineering and programming efforts of Dr James Beaumont, William Radke Bill Gilmore, and Dianne McClung

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The magnetic heart vector

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Electromotive forces (EMF) in the heart produce currents in the torso which set up a weak external magnetic field. This field can be measured by the use of pickup coils.[1-4] A major problem has been the presence of interfering fields from motors and other electrical equipment hundreds of times stronger than the peak field due to the heart (about one millionth of the earth's field) However by the use of additional coils fairly distant from the heart, this interference can be cancelled out to a considerable extent. With our present magnetocardiograph we are able to measure the heart's magnetic field in a hospital environment (New York State Upstate Medical Center) without the use of a magnetically shielded room These records are several times noisier than average conventional electrocardiograms (ECG's) Averaging 25 to 100 complexes provides records comparable in "cleanliness" to ECG's. Fig 1 shows an unaveraged magnetocardiogram along with the noise reduction achieved by averaging

We have been using a coil arrangement intended to provide magnetocardiograms similar in form to conventional x and y-lead ECG's. This was done primarily to establish that the magnetic records were not artifacts. A great deal of experimentation has now shown beyond doubt that the magnetocardiographic records reflect variations in the magnetic fields set up by currents induced by the heart's EMF's. Magnetocardiograms obtained on persons without heart disease do roughly mimic the appropriate ECG's. However in many subjects with heart disease (LVE's RVE's, infarcts) gross differences between the two types of records have been observed This and studies of the effect of differences in conductivity between heart and lung lead us to believe that with a different coil arrangement, magnetocardiography might furnish diagnostic data not present in the ECG

The heart is almost surrounded by lung whose electrical resistivity considerably exceeds that of the cardiac muscle and enclosed blood masses. Reported resistivity values are 2,000 ohms per centimeter for lung tissue 400 ohms per centimeter for ventricular muscle† and 160 ohms per centimeter for blood.[5] One result of these differences is that the heart and blood offer relatively low electrical resistance paths to tangential EMF's, i.e., electromotive surfaces so oriented that a vector perpendicular to them is directed tangentially

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†Ventricular muscle resistivity is anisotropic, being about 250 ohms per centimeter in the fiber direction and 550 ohms per centimeter across the fibers. The figure, 400 ohms per centimeter is used as rough "lumped" average.

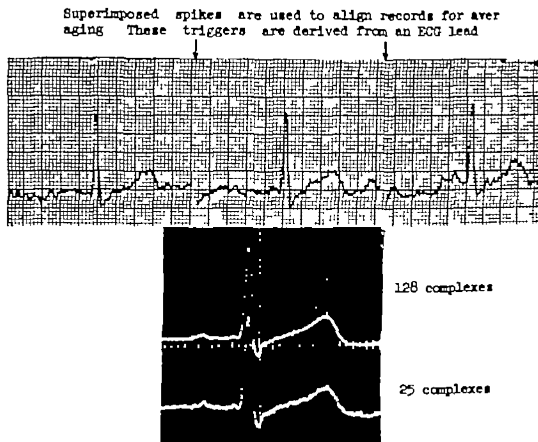


Fig 1 Signal averaging The top record shows three unaveraged complexes. The photograph on the bottom shows 25 and 128 averaged complexes. These records were obtained in a room in the New York State Upstate Medical Center some 20 meters from 30 large electric motors. The output of the coils has been integrated so the deflections register the magnetic flux and not the rate change of flux.

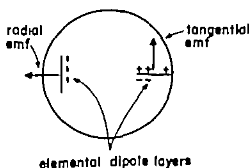


Fig 2 A tangential and a radial EMF Each elemental electromotive surface is represented by a vector perpendicular to its surface. The terms tangential and radial refer to the vector direction. The vector for a radial EMF is coincident with a line from the heart's center to its periphery The vector for a tangential EMF is perpendicular to such a line.

with respect to the heart's outer surface (Fig 2) Thus large circulating currents and magnetic fields will be produced by such tangential EMF's. In contrast, current flow from radial EMF components will be inhibited by the high resistance of the lung Given equal radial and tangential components, the latter will cause the larger magnetic field This situation is the opposite to that found in conventional ECG leads where because of the low resistivity of blood relative to heart muscle, radial EMF's are emphasized ("Brody" effect)[8] The net result is that magnetocardiographic leads tend to emphasize the tangentially oriented EMF's, which are usually masked in conventional electrocardiographic leads by the radial EMF's. In addition the magnetic measurements can be expressed as a magnetic heart vector analogous to the heart vector of vectorcardiography but radically different in interpretation

The latter part of the paper discusses magnetocardiography from the reciprocal or lead field point of view Here the concept of ideal magnetovectorcardiographic leads analogous to ideal electrovector cardiographic lea
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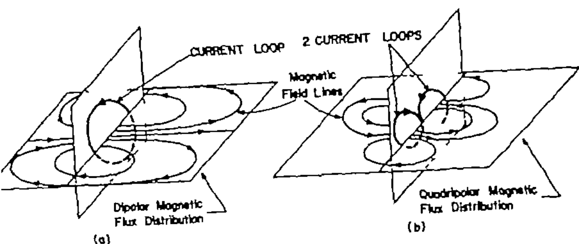


Fig 3 Magnetic flux distributions for one and two current loops. The magnetic flux distribution is sketched in one plane only

HOMOGENEOUS MODEL

INSULATING LUNG MODEL

HIGH RESISTIVITY LUNG MODEL

current flow distribution

magnetic flux distribution

flux leaves chest

flux enters chest

(a) (b) (c)

Fig 4 Current flow and magnetic field distributions. Each model shows tangential electromotive surface. For the homogeneous model on the top of the current flow consists of oppositely directed pairs of loops and the magnetic flux will be of the form shown in Fig 3 b. This magnetic field is sketched in relation to the torso in ( ) (bottom). If the lung is assumed to be an insulator the tangential EMS will cause unidirectional current loops resulting in magnetic flux of the form shown in Fig. 3, a, and again sketched in (b).

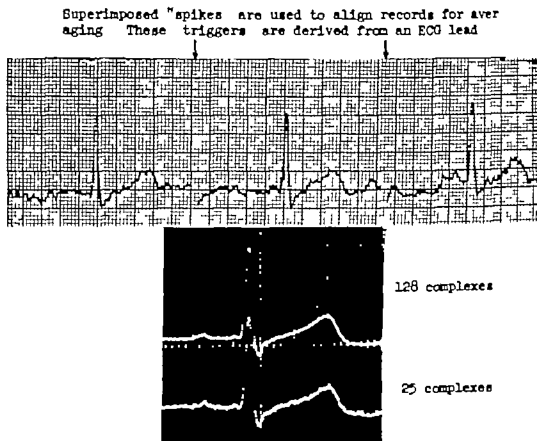


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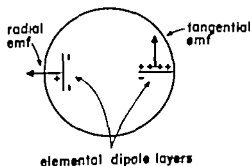


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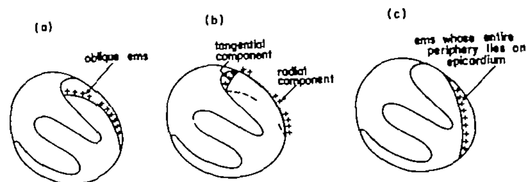


Fig 5 The decomposition of typical actn tion front into radial and tangential components. The wa front shown in ( ) has no tangential component.

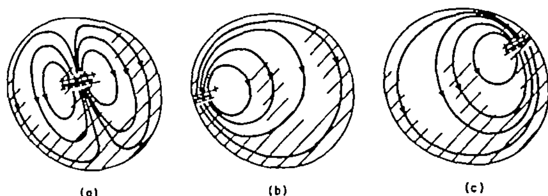


Fig 6 Current flow in the heart, hen the lung conductivity is considered negligible for elemental EMF located in the center right side and left side of the heart

netic field points out of the paper Thus the EMS to the right of center will give a deflection opposite to that left of center This is in contrast to a vectorcardiographic lead (ideally sensitive only to strength and orientation of an EMS) which will give the same deflection for the EMS illustrating the three cases.

It is possible to build a magnetic pickup system sensitive to the dipole magnetic field but not to the quadripole field. From the previous considerations, t is seen that such a pickup configuration will be sensitive primarily to the tangential components of the heart s electromotive surfaces, and that this sensitivity will be in proportion to the distance of the EMS from the center of the heart. Such a magnetocardiograph should provide information that differs substantially from that found with electrocardiography where the tangential components of the EMS are suppressed and the radial components are accentuated due to the intracavitary blood resistivity being lower than the ventricular muscle resistivity (' Brody" effect) We parenthetically note one other difference. The voltage in duced in electric leads is strongly influ enced by the low resistivity muscle layer around the torso This is not true for magnetic leads.

Fig 7 shows one possible apparatus for picking up the magnetic dipole and reject ing the magnetic quadripole due to current loops lying in the frontal plane. The subject lies between two fairly large high per meability disks. The disks are magnetically connected by the remainder of the high permeability structure. The two pickup coils are wound in the same direction. In Fig 7 *b* a single current loop is used to represent a magnetic dipole source and the

netovectorcardiography is shown Magnetovectorcardiograms will share one of the clinically important features of vectorcardiograms namely that given a well designed lead system accurate knowledge of the anatomical location of the heart is unnecessary

Elementary theory of magnetic leads

The elementary source of magnetic flux is a current loop Fig 3 *a* shows such a loop and its magnetic field At distances large compared to the size of the loop (in practice, one or two loop diameters) the shape of the magnetic field follows the well known dipole formula For example the magnitude of the magnetic flux goes down with the cube of the distance from the loop As a magnetic dipole source the exact shape of the current loop is unimportant and its dipole strength is IA where I is the loop current and A is the area enclosed by the loop Two current loops in close proximity equal in magnitude of strength but with opposing current directions form a quadripole source of magnetic flux. Such a configuration is shown in Fig 3 *b* along with a sketch of the quadripole magnetic field At remote points this field diminishes with the fourth power of the distance to the loops.

Consider two extremes of simplified heart lung models. In the first, all resistivities are considered equal and in the second the lung is considered to be a perfect insulator The difference in resistivity between muscle and blood will be ignored Fig 4 *a* and *b* illustrate these two cases and in each is shown an electromotive surface located in the outer part of the heart and perpendicular to the heart s periphery For the homogeneous model (Fig 4 *a*) the electromotive surface (EMS) causes a dipolar electric current flow throughout the heart and torso This current distribution is a smeared form of the two current loops shown in Fig 3 *b* and the resulting magnetic field will be of the magnetic quadripolar type. For the orientations of Fig 4 *a* magnetic flux will leave the chest on the left side of the heart, and re-enter on the right side

In Fig 4 *b* all current flow is within the heart, since the lung is assumed to be an insulator There will be no voltage drops anywhere on the body surface* i.e. the ECG will be silent. This current flow distribution resembles that of the single current loop of Fig 3 *a* and will give rise to a dipolar magnetic field Magnetic flux will leave the chest over the heart and re-enter the chest in a circular region around the heart. When the lung resistivity is higher than heart and blood resistivities, but not infinite the current distribution and magnetic field distributions can be considered, as a first approximation to be a mixture of the two extreme case distributions. This is illustrated in Fig 4 *c*

The electromotive surface in the ventricular walls is seldom purely tangential. It is often oblique as shown in Fig 5 *a* with a radial component parallel to the epicardial surface as well as a tangential component from endocardium to epicardium Such an EMS can be replaced by an equivalent surface consisting of a radial component and a tangential component, as is shown in Fig 5 *b*† The component coincident with the heart lung boundary will not cause currents to circulate within the heart and will not give rise to the dipolar form of magnetic field Note also that an EMS whose entire boundary lies on the epicardium (Fig 5 *c*) has no tangential component since it can be replaced by an equivalent surface entirely coincident with the heart lung boundary An EMS in the center of the heart as might arise for example from septal depolarization will cause a quadripolar rather than a dipolar magnetic field even assuming the lung to be an insulator (Fig 6 *a*) As the EMS is moved from the center to the periphery of the heart maintaining an orientation perpendicular to the periphery the opposing loop pairs of current flow change to unidirectional loops. The magnetic field will change from the quadripolar to the dipolar form In Fig 6 *b* where the EMS lies to the right of center the current circulates clockwise and the magnetic field is directed into the paper In Fig 6 *c* the EMS lies to the left of center the current circulates counterclockwise and the mag

*Assuming the muscle layer around the torso is not an insulator

†The complete equivalency of the two surfaces follows from theorem by Gauss. A completely closed uniform electromotive surface causes no current flow This is true even for nonhomogeneous and nonisotropic volume conductor

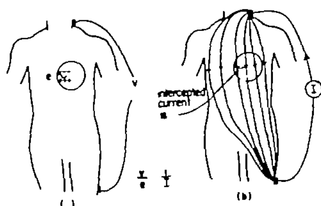


Fig 9 An example illustrating the use of reciprocity for an electrocardiographic lead.

lines of magnetic flux due to this source as they travel through the magnetic structure are sketched. Flux travels through the cores of the two coils and induces additive voltages. In Fig 7 *c* two loops of current are used to represent a magnetic quadripole source. The lines of magnetic flux are again sketched. No flux passes through the windings and hence there is no output.

The magnetic heart vector

The heart vector of electrovectorcardiography has three components one along the x axis (right side to left side) one along the y axis (head to foot) and one along the z axis (front to back) The magnetic heart vector may also be viewed qualitatively as arising from three components a current circulating in the heart about the x axis and two other currents circulating about the y and z axes, respectively where each of the circulating currents is established by tangential components of the heart's EMF's. This is shown in Fig 8 *b* through *d*. These three circulating currents may each be represented by a vector along the axis of circulation with a magnitude proportional to the strength of the circulation and a polarity determined according to the right-hand rule. The sum of these three vector components is the total spatial magnetic heart vector For example, Fig 8 *e*, shows a current loop 45 degrees to all axes and its representative vector V Fig 8 *f* shows the three components of vector *V* namely V_x, V_y, and V_z. These components represent current flows around the x y and z axes, respectively Since vector *V* was chosen to have equal lengths on all three axes, the three component current loops are of equal strength as shown in Fig 8 *g* As in vectorcardiography the vector representing the magnetic dipole current will change in direction and strength throughout the depolarization and repolarization cycle. Any of the display systems of vectorcardiography can be applied to magnetovectorcardiography

Magnetic heart vector lead fields The interpretation of magnetocardiograms and the design of appropriate magnetic pickup configurations, is greatly simplified by the use of the reciprocal or lead field method.[6-8] The extension of the electrocardiographic lead field method to magnetocardiography is given in reference 9 A brief nonmathematical review is given here.

To illustrate the lead field concept as used in electrocardiography consider a y-lead ECG (Fig 9) Fig 9 *a* shows the electromotive surface of the heart across which there is a uniform potential difference *e*. Due to this EMS, there is a voltage *v* across the two wires which go to the recorder input. Because of the complicated boundary conditions the visualization of how voltage *v* is related to the EMS and the location of the electrodes upon the body is not always easy Fig 8 *b* illustrates the reciprocal or lead field method. The

*Curl the fingers of the right hand and extend the thumb. Consider the fingertips to be arrowheads. When the curled fingers point in the direction of current flow the thumb points in the direction of the loop vector.

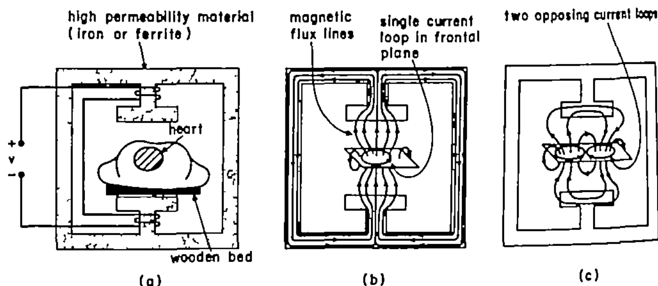


Fig 7 An example of a magnetic pickup assembly that will register a dipolar magnetic field and not register a quadripolar magnetic field For clarity the coils have been omitted from (*b*) and (*c*). The single loop of (*b*) causes flux through coils causing an output voltage. For two opposing loops there is no flux through the coils

(a) VCG reference system

(b) current loop circulating about Y axis (in horizontal plane)

(c) current loop circulating about X axis (in sagittal plane)

(d) current loop circulating about Z axis (in frontal plane)

(e) vector ⊥ to plane of loop

(f) 3 components of vector V

(g) 3 components of loop

Fig 8 The magnetic heart vector Parts (*b*) (*c*), and (*d*) show current loops in three orthogonal planes. Each is represented by a vector directed along the axis of circulation. The [illegible]ector direction is determined using the right-hand rule. The [illegible]ector strength is proportional to the current strength times its distance from the axis of circulation (analogous to torque in mechanics). Part (*e*) shows a spatial current loop (taken 45 degrees t[illegible] each axis) and its vector representation. The components, [illegible]ector and loop, are shown in (*f*) and (*g*).

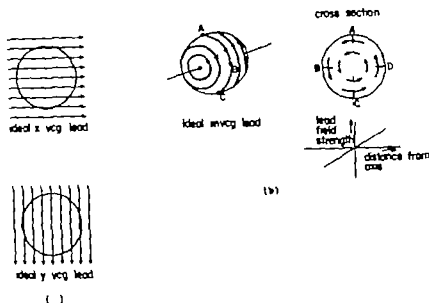


Fig. 11. Ideal magnetovectorcardiographic lead fields. For comparison, ( ) shows the uniform lead fields associated with ideal electrovectorcardiographic leads. The lead field of an ideal magnetovectorcardiographic lead (*b*) consists of circular current flow around an axis and confined to planes perpendicular t that axis. The lead field strength is zero at the axis and increases in proportion to the distance from it. The strength does not depend on the direction from the axis, i.e., it is the same for *A*, *B*, *C*, and *D* of (*b*).

tercepted by the electromotive surface. By use of the reciprocity theorem the ratio of the intercepted current i to the current I fed into the pickup coil is the same as the ratio of the voltage v measured across the pickup coil due to the potential e across the electromotive surface of the heart. The induced currents then constitute the lead field which is produced magnetically.

This lead field is determined by anatomical boundaries between tissues of different resistivities (including the outside torso-air boundary) and by the magnetic pickup configuration. This statement is analogous to the statement that the lead field in electrocardiography is determined by the torso boundaries and the number and location of electrodes placed on the torso. Because of this close analogy the disks of the pickup units from which magnetic flux leaves or enters might well be called "magnodes"; thus the number and location of the magnodes and the torso geometry determine the lead field. Both arrangements of electrodes and arrangements of magnodes can be characterized completely by the lead field which they produce.

There is one major difference between the lead field which can be produced by magnetic electrodes (magnodes) and those which can be produced by conventional electrodes. For electrodes, the lines of current flow must begin and end on electrodes. In contrast to this, the magnetic lead field consists of currents which swirl around without starting at surface electrodes.

Ideal lead field for magnetovectorcardiography. Since the electromotive surface representing the activation boundaries lies in the heart, electrocardiographic or magnetocardiographic lead fields need only be known within this region. The ideal electrovectorcardiographic lead is one which is uniform throughout the heart region. Three such leads, orthogonal and of equal strength, are required. Ideal x and y vectorcardiographic leads are illustrated in Fig. 11, *a*. Due to their uniformity they are sensitive only to the strength and orientation of an elemental electromotive surface, but not to its position, i.e., there are no "proximity effects."

A magnetovectorcardiographic lead field will be considered ideal if it consists of essentially circular flow lines, zero on an axis through the center of the heart, and

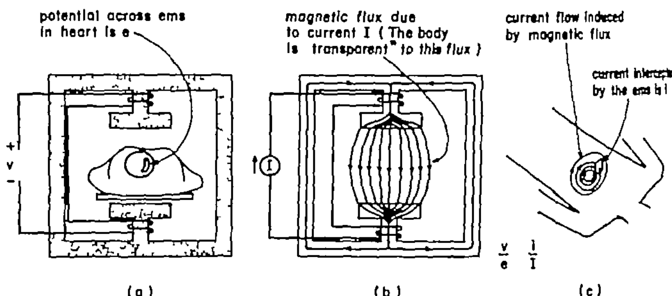


Fig 10 An example illustrating the use of reciprocity for a magnetic lead. The lead field is the current that would be magnetically induced in the torso if a fluctuating current I were passed through the pickup windings.

potential e across the electromotive surface is first set to zero A current I is then injected into the lead that was previously labeled minus and a current I removed from the lead that was previously labeled plus. The distribution of this current as it flows through the body is the lead field A certain percentage of the injected current denoted by i is intercepted by the electromotive surface. By the reciprocity theorem it can be shown that the ratio of the intercepted current to the injected current is identical to the ratio of the voltage at the recorder input to the voltage across the EMS that is

$$\frac{v}{e} = \frac{i}{I}$$

The advantage to this method of attack is that it is easy to visualize the lines of current flow or lead field" within the body

In magnetocardiography we are interested in the voltage produced across the pickup coil winding as a result of the EMS of the heart. This relation can be obtained by putting a current I into the pickup coil and finding the resultant current i intercepted by the electromotive surface under consideration.

The magnetic assembly of Fig 7 is used as an example. To make a direct evaluation of the voltage across the coil winding one must first find the current field in the body which is produced by the electromotive surface then find the magnetic field due to this current taking into account the fact that it will be distorted by the high permeability iron of the pickup assembly The portion of the magnetic field passing through the winding will induce a voltage in it which is proportional to the rate change of the field

In the reciprocal method we go through a sequence of steps illustrated in Fig 10. The electromotive potential e of the heart (Fig 10 a) is first set equal to zero. A fluctuating current I is (conceptually) injected into the pickup winding This current causes a magnetic flux to emanate from the disk above the chest, to flow through the torso and enter the disk beneath the back* This flow of magnetic flux through the torso induces eddy currents therein as shown by the circular flow lines in Fig 10 c (The secondary magnetic field caused by the eddy currents is negligible for typical tissue resistivities.) These induced currents are proportional to the rate change of flux through the torso and thus require that the initial injected current I be changing with time if there is not to be a zero result Some of this induced current, denoted by i is in

*The permeability of the body tissues differs little from free space, i.e. the torso is "transparent" to magnetic flux.

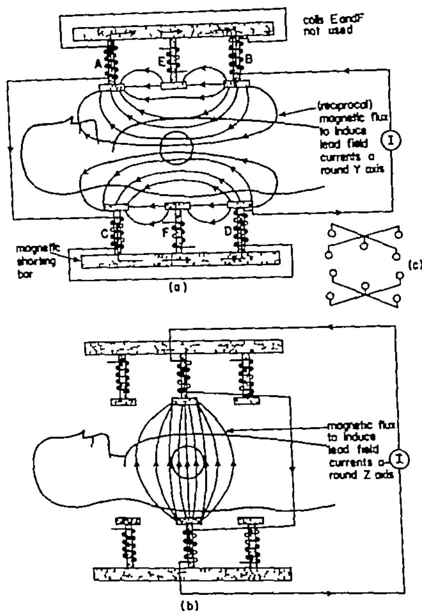


Fig. 14 A coil configuration capable of measuring all 3 components of the magnetic heart ector The subject is lying on nonmagnetic bed (not shown). From the reciprocal point of view energizing coils *A B C*, and *D* in part ( ) will result in uniform magnetic flux in the heart region directed from foot to head and inducing the y magnetovectorcardiographic lead. With an appropriate pivot on the bed, the subject can be rotated 90 degrees so the magnetic flux passes from right to left, inducing an directed lead. Energizing coils *E* and *F* will result in directed lead, as show in (*b*).

nodes B and D Magnodes E and F are not energized. The resulting magnetic flux distribution is sketched in Fig 14 *a* At the structure s center the magnetic field distribution is directed from head to foot and is quite uniform. The induced lead field current flows in planes perpendicular to the magnetic flux, i.e., the subject s "horizontal" plane. By rotating the subject 90 degrees, still lying on his back, the lead field current will be in sagittal planes.

A magnetic flux distribution directed from front to back and uniform in the heart region is generated by energizing coils E and F such that flux leaves E and enters F This induces lead field current in the

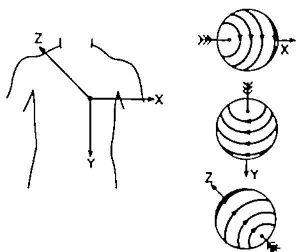


Fig 12 Three orthogonal leads for the magnetic heart vector

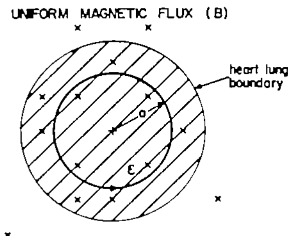


Fig 13 A uniform magnetic flux will induce an ideal magnetovectorcardiographic lead field.

increasing linearly in strength towards the periphery (Fig 11 *b*) This lead is sensitive only to tangentially oriented elemental electromotive surfaces. There are no proximity effects in the sense that the output due to a tangential EMS will depend only on its distance from the axis e g surfaces A B C and D of Fig 11 *b* will give equal outputs. For a complete magnetovector cardiogram three such lead fields are needed mutually orthogonal and of equal strength This is illustrated in Fig 12

To the extent that the heart can be represented by a homogeneous sphere imbedded in a high resistivity lung there is a simple criterion for generating ideal magnetovectorcardiographic leads. Considered reciprocally current into the coils of the magnetic pickup should produce a uniform magnetic field in the heart region. Note that this was the case for the example of Figs 7 and 10 In the presence of a uniform (time-varying) magnetic field the heart lung boundary will result in circular lead field flow lines centered in the heart, and lying in planes perpendicular to the magnetic flux Using Faraday's law that the line integral of the electric force around a closed loop is equal to the rate change of the enclosed flux $\int E \cdot d\ell = d/dt \iint B \cdot dA$, it can be seen that the lead field strength increases in proportion to the distance from the heart center Since B is constant (Fig 13) the enclosed flux for a loop of radius a is $(\pi a^2)\beta$ and thus

$$\int E\, d\ell = 2\pi a\, E = \pi a^2 \frac{dB}{dt}$$

$$J = \frac{1}{\rho} E = \left(\frac{1}{2} a\right) \frac{dB}{dt}$$

where ρ is the resistivity of the heart. Note that the exact anatomical location of the heart need not be known for the lead field to center itself Self-centering will occur so long as the lung conductivity is negligible and the heart may be considered to be spherically homogeneous and to be within the region of uniformity of the magnetic flux produced by the reciprocally energized coils. This is analogous to the case for ideal vectorcardiographic leads, where lead design can make the location of the heart noncritical by insuring a sufficiently large region of uniform lead field current

Design of a magnetic pickup suitable for magnetovectorcardiography The magnetic pickup configuration previously discussed (Fig 7) is suitable for inducing an ideal magnetovectorcardiographic lead field in the frontal plane and by turning the subject on his side the sagittal plane It would be difficult to implement for the horizontal plane. Fig 14 shows a structure suitable for all 3 planes. It consists of 6 magnodes, 3 above the chest and 3 beneath the back The distal ends of the upper magnetic pickup units are connected by a magnetic shorting bar The same is true for the bottom units. The 4 corner coils A B C and D are connected in series and the winding directions are such that when energized magnetic flux will leave magnodes A and C an ag

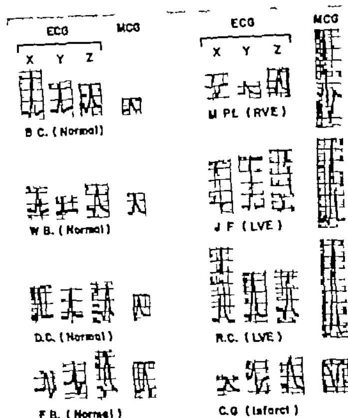


Fig. 17. Magnetocardiograms obtained with magnetic lead that emphasizes tangential EMF's. The first column shows 4 subjects from series of 20 with the magnetocardiograms ordered from smallest to largest. The second column show the 4 (out of 20) subjects with heart disease for whom the single coil lead deflections were most abnormal. The ECG were obtained with the axial lead system. All records are t 50 mm. per second and the ECG are t 10 mm. per millivolt. All magnetocardiograms are taken at the same gain as determined by calibration coil.

frontal plane. If desired all 3 leads could be obtained simultaneously by the use of ten coils. The arrangement of these 10 coils is shown schematically in Fig. 14 c.

Some preliminary measurements of tangential EMF's. A pickup unit in our present magnetocardiograph consists of a 1.6 cm. diameter ferrite rod 30 cm. long capped on each end with a ferrite disk 6 cm. in diameter. A pickup coil of 5,000 turns is wrapped around the ferrite rod. Fig. 15 *a* shows such a unit over a homogeneous resistive slab with a top boundary ("chest") and a bottom boundary ("back") but no side boundaries. It is easily shown[11] that the induced lead field current will flow in circles around an axis perpendicular to the front (and back) boundaries and centered underneath the pickup unit. The circular lead field shape is but little altered by the boundaries corresponding to the torso sides, top and bottom,[11] or consideration of the resistivity differences between heart and lung. This "magnetic lead" thus measures tangential EMF components lying in frontal planes.

The present magnetocardiograph[11] designed primarily to duplicate ECG's has two such pickup units 20 cm. apart. The above "single coil lead" is approximated by placing the heart under one of the two coils (labeled A in Fig. 15 *b*) with the other (labeled B in Fig. 15 *b*) positioned beyond

*There are actually four units. Two of these are used only to cancel interfering fields and are sufficiently far from the heart that they can be ignored with regard to the cardiac magnetic field. The need to cancel interference also explains why the "single coil lead" is not realized by removing coil B of Fig. 15, *b*, entirely. When the heart is centered between the two coils it lies in approximately uniform lead field and hence the magnetocardiograms should be comparable to ECG obtained with vectorcardiographic leads.

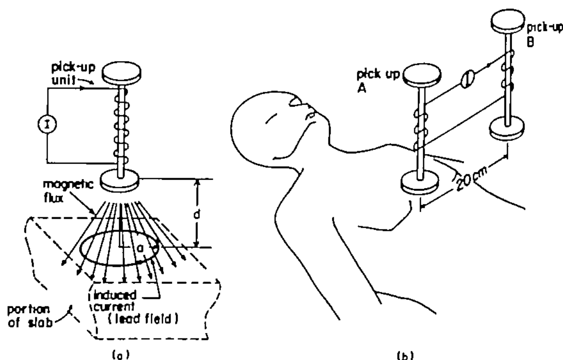


Fig 15 The "single coil lead of our present magnetocardiograph (*a*) The lead field current for a single pickup unit flows in circles centered under the pickup. The lead field strength is zero at the center and increases with radius *a* so long as *a* is less than $\sqrt{2}$ d (*b*) The present magnetocardiograph has two pickup units 20 cm. apart. In the records of Fig 16 coil A is placed over the heart region (fifth intercostal space and 2 cm. left of the sternal margin) and coil B is beyond the left boundary of the torso. Here the influence of coil B on the lead field in the heart region is small and the lead field will be approximately that described in (*a*). This lead is sensitive primarily to tangential EMF's.

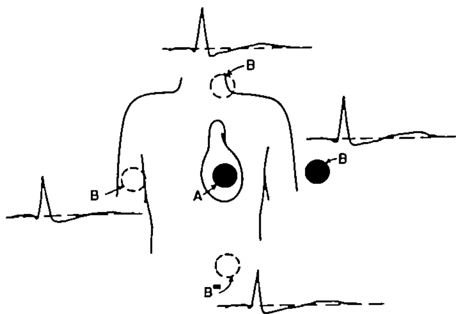


Fig 16 A test of the influence of coil B Coil A remains centered over the heart, while B is moved from the left side location to a location over the neck right side and abdomen. The magnetocardiogram obtained at each position for a normal subject shows little change. This was true for all persons (5) so tested. In every subject a record taken with coil B over the right side was compared to that obtained with coil B over the left side. There were no large discrepancies. The S-T segment depression is due to the poor (0.3 cycle per second) low frequency response of the magnetocardiogram.

Effects of isoproterenol infusion on myocardial structure and composition*

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The clinical use of isoproterenol as a beta-adrenergic stimulator is increasing. However, there are numerous experimental studies demonstrating myocardial necrosis and compositional alteration associated with large doses of isoproterenol.

This is a report of the effects of chronic isoproterenol infusion on myocardial structure and composition.

Methods

Six mongrel dogs, weighing 8 to 17 kilograms, were anesthetized with sodium thiopental (Pentothal) 40 mg. per kilogram and mechanically ventilated with room air. A Silastic catheter was introduced into the jugular vein and tunneled subcutaneously to emerge at the back of the neck. The catheter joined the battery-operated electric infusion pump (Sigma motor ML 5) containing a 6½ days' supply of medication. This unit was carried in a harness so that the animals could be allowed normal activity and alimentation. Isoproterenol was infused at a constant rate of 1.5 µg per kilogram per hour for six days. The animals were put to death with intravenous sodium secobarbital (Eunol) 100 mg. per kilogram and the hearts promptly excised and placed in cracked ice. Tissue was obtained for electron microscopy. The hearts were subdivided into five segments corresponding to the chambers and the interventricular septum and weighed. Myocardial samples were prepared for light microscopy and samples of the remainder were homogenized for chemical and enzymatic analysis. Catecholamines were assayed according to the method of Crout and associates. Total carbohydrates were determined by the direct anthrone method and glycogen by the anthrone reaction[1] after isolation of glycogen from the KOH digest. Unesterified fatty acid extractions and titrations were done by the method of Dole and Meinertz and saponification procedures for total fatty acid determinations were those of Albrink. The phosphate content of the lipid fraction was analyzed according to the method of Youngberg and Youngberg[4] using the phosphate procedure of Fiske and Subbarow. Values were expressed as milligram of lecithin equivalents per gram of tissue. Sodium and potassium were read in a Coleman flamephotometer after the sam-

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the left side of the torso Fig 16 shows a test of the influence of coil B made by rotating the subject (the specially made bed had a pivot point for this purpose) such that coil A remained fixed over the heart and coil B assumed positions over the left side the head the right side and the abdomen If the influence of coil B were completely negligible the magnetocardiograms for the four positions would be identical The observed change was on the order of 5 to 15 per cent.

Fig 17 shows magnetocardiograms obtained for the single coil lead i e frontal plane tangential EMF's, along with x y and z lead ECG s (axial system) The first column of four records are from a group of 20 normal subjects. Fifteen normal subjects had entirely upright QRS deflections with 5 having a small negative terminal deflection (e.g F B) The smallest amplitude normal magnetocardiogram was from subject B C and the largest from F B From a group of 20 subjects with heart disease 4 had strikingly abnormal deflections for the single coil lead These are shown in the second column of Fig 17 The magnetocardiogram for subject M Pf with right ventricular enlargement shows a large negative terminal deflection in addition to a larger than normal upright deflection Subjects J F and R C have aortic insufficiency (LVE) Here the magnetic record amplitude has increased much more markedly than the electrocardiographic voltages. For infarct subject C G the magnetic deflection was entirely negative

Summary

Records of the magnetic field due to the heart can be obtained in a hospital environment without the use of a magnetically shielded room It is possible to build a magnetocardiograph sensitive primarily to the tangential components of the heart s EMF's. This is in contrast to ECG s where the radial component is emphasized and usually masks any tangential components. Tangential EMF components lying in frontal planes cause current to circulate around the front to-back (z) axis and can be assigned a vector direction along this axis Similarly tangential EMF's in sagittal and horizontal planes can be associated with x and y directed vectors. The vector sum of these three components is the spatial magnetic heart vector The magnetic heart vector is conceptually similar to and can be displayed using the same techniques as, the heart vector of electrovectorcardiography but is of radically different interpretation

Ideal magnetocardiographic leads, analogous to ideal electrovectorcardiographic leads are defined in terms of the lead fields produced Our present magnetocardiograph while not specifically designed to implement the ideas of this paper does give evidence that there are some tangentially oriented EMF components in persons without heart disease, and often much larger tangential EMF's in persons with heart disease.

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Table I. Myocardial analysis

Substance	*Unit*	*No. of hearts*	*Right ventricle*	*Left ventricle*	*Interventricular septum*
Sodium	µEq/Gm.	6	39.0 ± 3.0	41.0 ± 2.71	39.6 ± 2.68
Control		22	43.93 ± 1.27	44.17 ± 1.77	43.38 ± 1.46
Potassium	µEq/Gm.	6	76.3 ± 1.16	79.8 ± 1.57	77.3 ± 1.53
Control		22	76.16 ± 0.88	78.13 ± 1.15	76.89 ± 1.37
Total carbohydrate	mg./Gm.	6	2.08 ± 0.14	1.72 ± 0.12	1.35 ± 0.14
Control		22	4.84 ± 0.59	4.53 ± 0.51	4.13 ± 0.57
Glycogen	mg./Gm.	6	0.27 ± 0.12	0.24 ± 0.05	.08 ± 0.05
Control		21	3.92 ± 0.63	3.33 ± 0.56	3.26 ± 0.59
Total lipid	µEq/Gm.	6	121.8 ± 23.2	66.0 ± 4.8	58.2 ± 5.2
Control		22	130.5 ± 22.9	69.2 ± 4.5	60.7 ± 3.5
Phospholipid	mg./Gm.	6	25.98 ± 0.82	26.30 ± 0.26	27.20 ± 0.82
Control		22	24.03 ± 0.58	25.97 ± 0.52	26.73 ± 0.63
Unesterified fatty acids	µEq/Gm.	6	19.6 ± 2.0	16.8 ± 1.75	17.0 ± 1.62
Control		22	15.76 ± 1.27	15.61 ± 0.93	16.29 ± 0.96
Catecholamines	µg/Gm.	6	0.53 ± 0.1	0.48 ± 0.1	0.51 ± 0.1
Control			0.54 ± 0.08	0.55 ± 0.07	0.62 ± 0.07

Table II. Myocardial enzyme activity (in µmoles per minute per gram of protein)

Enzyme	*N of hearts*	*Right atrium*	*Right ventricle*	*Left atrium*	*Left ventricle*	*Interventricular septum*
Glucose-6-phosphate dehydrogenase	6	6.8 ± 1.12	2.6 ± 0.4	4.2 ± 0.27	2.1 ± 0.71	2.0 ± 7.8
Control	21	4.65 ± 0.30	2.03 ± 0.2	2.03 ± 0.25	1.63 ± 0.1	1.73 ± 0.15
Phosphofructokinase	5	82.8 ± 16.3	98.8 ± 24.3	114.5 ± 20.9	74.5 ± 10.3	74.1 ± 12.7
Control	11	100.0 ± 17.7	100.0 ± 17.3	100.0 ± 8.7	100.0 ± 19.4	100.0 ± 18.9
Glycerophosphate dehydrogenase	6	179.0 ± 5.8	177.3 ± 20.2	198.0 ± 13.3	177.1 ± 20.1	128.6 ± 12.1
Control	21	114.4 ± 9.1	132.4 ± 16.8	127.8 ± 7.6	150.4 ± 8.3	123.4 ± 6.3
Triosephosphate isomerase*	5	86.4 ± 8.5	97.8 ± 13.1	108.0 ± 4.4	100.2 ± 8.6	124.8 ± 11.1
Control	11	100.0 ± 6.7	100.0 ± 5.8	100.0 ± 8.8	100.0 ± 4.7	100.0 ± 4.9
Aldolase*	5	98.0 ± 10.2	99.9 ± 21.5	90.4 ± 17.0	103.4 ± 9.7	118.9 ± 8.4
Control	11	100.0 ± 11.1	100.0 ± 9.4	100.0 ± 11.3	100.0 ± 10.8	100.0 ± 10.0
Phosphoenolpyruvate kinase	6	61.7 ± 6.7	75.0 ± 7.8	63.2 ± 12.1	64.9 ± 1.8	85.3 ± 8.3
Control	10	41.7 ± 3.9	63.2 ± 4.0	35.4 ± 4.8	64.8 ± 5.0	65.9 ± 4.5
Lactic acid dehydrogenase†	6	4.5 ± 0.35	3.4 ± 0.16	2.7 ± 0.35	2.5 ± 0.42	2.6 ± 0.23
Control	21	2.24 ± 0.29	2.22 ± 0.17	1.92 ± 0.15	2.41 ± 0.13	2.23 ± 0.14
Cytoplasmic malic enzyme	6	61.7 ± 11.8	24.7 ± 4.2	43.0 ± 8.4	21.2 ± 4.4	21.2 ± 4.2
Control	11	27.7 ± 6.0	19.3 ± 3.1	27.7 ± 4.2	18.4 ± 3.0	19.4 ± 3.2
Isocitric dehydrogenase	6	35.8 ± 3.7	30.3 ± 2.7	34.0 ± 3.0	42.4 ± 10.3	44.6 ± 5.1
Control	18	24.6 ± 1.8	31.8 ± 2.3	24.1 ± 2.1	31.0 ± 2.8	34.0 ± 2.9
Fumarase	6	31.7 ± 6.7	40.2 ± 4.8	24.0 ± 5.6	43.8 ± 10.1	63.3 ± 10.3
Control	20	35.6 ± 4.6	41.8 ± 5.7	23.6 ± 3.9	47.6 ± 5.3	47.3 ± 6.4
Mitochondrial malic enzyme	6	41.5 ± 9.1	21.8 ± 1.8	44.6 ± 9.3	34.6 ± 7.7	25.9 ± 6.6
Control	23	41.4 ± 3.9	23.1 ± 2.2	47.4 ± 3.9	28.7 ± 2.2	25.9 ± 1.7
Malic dehydrogenase	6	1068.0 ± 301.0	603.0 ± 206.9	687.0 ± 180.0	513.0 ± 85.0	584.0 ± 87.0
Control	14	593.5 ± 61.6	685.4 ± 32.6	456.0 ± 64.0	307.0 ± 30.0	333.0 ± 33.0

*Aldolase and triosephosphate isomerase activities are expressed as per cent of normal.
†LDH activity is expressed in moles per minute per milligram of protein.

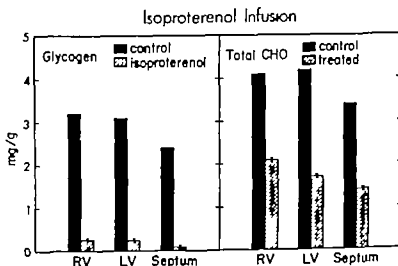


Fig 1 Myocardial glycogen content is shown on the left and total carbohydrate content on the right

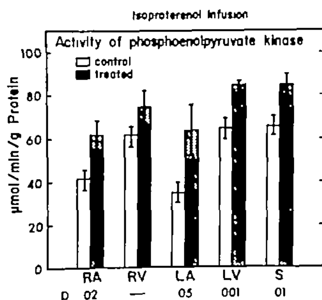


Fig 2 Isoproterenol infusion is associated with an increase in activity of phosphoenolpyruvate kinase in all chambers.

ple was dissolved in acetic acid Enzymatic assays were carried out by standard methods.[7]

Results

The ratio of heart weight to body weight, grams per kilogram was 7 87 ± 0 98 for the control animals and 7 96 ± 0 72 for the treated animals.

The results of myocardial analysis for sodium potassium glycogen total carbohydrate total lipid phospholipid unesterified fatty acids and catecholamines are summarized in Table I These values were normal except for myocardial glycogen depletion which accounts for the decrease in total carbohydrate (Fig 1)

The results of myocardial enzyme analysis are summarized in Table II The activities of these enzymes were in the normal range with the exception of phosophoenolpyruvate kinase which was statistically significantly increased in all segments but the right ventricle (Fig 2) and increased activity of a few enzymes in one or two myocardial segments. The location of these enzymes in various metabolic pathways is shown schematically in Fig 3

Myocardial structure and ultrastructure were normal except for glycogen depletion which can be appreciated by comparing control myocardium (Fig 4) and treated myocardium (Fig 5)

Discussion

The dosage of isoproterenol was in the low range when compared to previous experimental and clinical studies of the physiologic effects of this amine (Table III) in which the infusion was continued for a few minutes to a few hours [8-14]

Cardiac hypertrophy did not develop in contrast to hearts exposed to large doses of isoproterenol in which initial cardiac enlargement was related to edema and later to increases in cardiac protein and nucleic acids.[15]

Hearts from animals receiving large doses of isoproterenol have shown increased Na^{++} Ca^{++} and Cl^{-} and de-



Fig. 4 Electron photomicrograph of control myocardium showing abundant glycogen granules and normal structure

Fig. 5 Electron photomicrograph of treated myocardium revealing depletion of glycogen granules and normal structure.

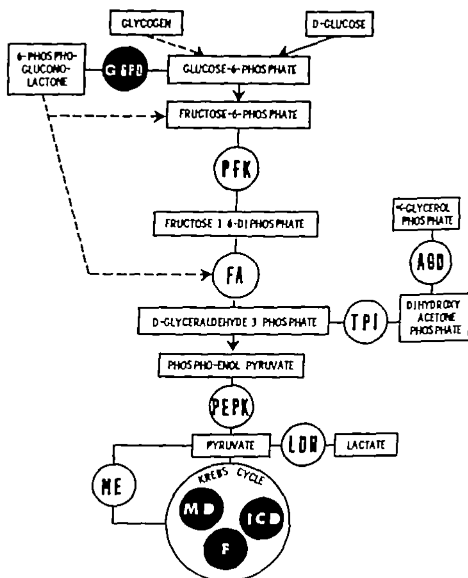


Fig 3 The enzymes that were assayed are shown in this abbreviated metabolic scheme. *G-6PD* Glucose-6-phosphate dehydrogenase *PFK* phosphofructokinase *FA* fumarase; *AGD* d-glycerophosphate dehydrogenase; *TPI* triosephosphate isomerase *PEPK* phosphoenolpyruvate kinase *LDH* lactic acid dehydrogenase *ME*, malic enzyme *MD* malic dehydrogenase *ICD* isocitric dehydrogenase *F* fumarase

Table III *Isoproterenol infusion**

Author	*Dosage (μg/Kg/h)*	
	Canine	*Clinical*
Bauer[4]	6-180	1 7-3 4
Benchimol[7]		1 7
Brown		7 0
Krasnow[11]	2 0-24	0 7-4 8
Mueller[12]		1 7-4 3
Silberschmid[13]	2 0-10	
Weissler[14]		0 9
Present study	1 5	

*Except in the present study these infusions were continued for few minutes to several hours while physiologic ob- ... made

creased Mg^{++} K^+ was slightly increased by smaller doses of isoproterenol (1 to 5 mg per kilogram) and decreased by a larger dose (80 mg per kilogram) [13] In those hearts catecholamine content was unchanged but catecholamine concentration was decreased [13]

Myocardial carbohydrate depletion was limited to glycogen and did not involve other carbohydrate fractions (Fig 2) A large injection of isoproterenol results in initial glycogen depletion while four days after treatment there is an increased amount of myocardial glycogen [14] Presumably glycogen depletion is due to glycogenolysis from phosphorylase activation The significance of the



Fig. 4 Electron photomicrograph of control myocardium showing abundant glycogen granules and normal structure.

Fig. 5 Electron photomicrograph of treated myocardium revealing depletion of glycogen granules and normal structure.

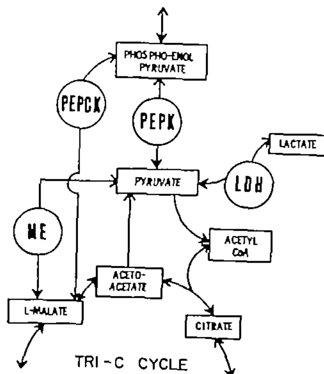


Fig 6 This metabolic scheme indicates the pathways for breakdown of phosphoenolpyruvate and its synthesis via the dicarboxylic acid shuttle. *PEPCK* Phosphoenolpyruviccarboxylase kinase.

tivity of phosphoenolpyruvate kinase is uncertain It may be secondary to glycogenolysis. On the other hand it may be contributing to glycogen depletion by competition with substrate for glycogen synthesis. The direct phosphorylation of pyruvic acid to phosphoenolpyruvate may occur under ideal conditions[17] but the dicarboxylic acid shuttle is considered to be the preferential pathway for lactate and amino acids to contribute to glycogen synthesis (Fig 6) Formation of phosphoenolpyruvate through the shuttle may be followed by its conversion to pyruvic acid rather than by glycogen synthesis. Considerable additional information is necessary to determine the dynamics of these reactions.

Chronic infusion of a small dose of isoproterenol was not associated with the severe alterations in myocardial structure and composition occurring after one or two injections of a large dose of isoproterenol The major alteration glycogen depletion diminishes the reserve of the myocardium for anaerobic metabolism but loss of this capacity is probably not of great pragmatic significance.

Summary

Six ambulatory dogs had continuous infusion of isoproterenol 1 5 μg per kilogram per hour for six days. The animals were put to death and the hearts excised and subdivided into five segments corresponding to the chambers and the interventricular septum The myocardium was studied by light and electron microscopy and analyzed for one enzyme of the hexosemonophosphate shunt seven enzymes of the glycolytic pathway three enzymes of the Krebs cycle total lipid phospholipid, unesterified fatty acids glycogen total carbohydrate catecholamines, sodium, and potassium Twelve normal dogs served as controls

Myocardial structure and ultrastructure were unaltered except for depletion of glycogen granules. Compositional alterations were limited to glycogen depletion (control 3 5 and treated 0 2 mg per gram) and increased activity of phosphoenolpyruvate kinase (control 54 0 and treated 73 9 μmoles per minute per gram of protein) Prolonged infusion of a small dose of isoproterenol is not associated with the myocardial necrosis and profound compositional alterations occurring after large doses of this amine

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Determination of interarterial coronary anastomosis by radioactive spherules Effect of coronary occlusion and hypoxemia

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The collateral coronary circulation is all important at the time of an occlusion because if functional it could reduce the extent of myocardial ischemia and thus limit the size of the infarct. Maintenance of this collateral circulation could also avoid asynergy of myocardial contraction which results in the dreaded complication of cardiac decompensation and shock [1-8] Considerable debate continues on whether the collateral coronary circulation is functional in a physiological sense prior to coronary artery occlusion [1, 7, 17] Previous investigators demonstrated an interarterial anastomosis at autopsy in both normal and arteriosclerotic hearts but they used nonphysiological techniques by injecting heavy lead agar material at a high perfusion pressure in the nonbeating heart. Their investigative techniques might have torn open unnatural channels and actually demonstrated artifact. There is general agreement that an interarterial collateral circulation developed following coronary occlusion in the dog and human [18-20] However there is disagreement whether such anastomosis is functional prior to occlusion Most agree it does not exist in the human but believe it is functional in the dog [4, 9, 16, 17, 21-24] The controversy could not be resolved until more physiologic techniques could be developed for study in the beating dog's heart.

Radioactive beads in graded sizes recently became available which could trace the collateral circulation and delineate the size of the anastomotic channels.[24,25] Experiments were designed to determine

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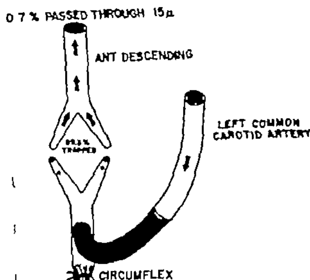


Fig. 1. Schematic drawing of method by which radioactive spherules suspended in Carbopol were introduced into a branch of the circumflex coronary artery and recovered from the adjoining anterior descending coronary artery under normal physiologic pressures. A branch of the circumflex was tied off and a cannula inserted to perfuse it with blood from the common carotid artery. Spherules were inserted into the connecting cannula. Retrograde blood was collected from the cut end of the anterior descending coronary artery. Radioactive counting indicated the amount of spherules which crossed between the arteries.

possible existence of such channels in the beating dog's heart immediately, 21 to 42 and 49 to 84 days after coronary ligation. In addition, experiments were conducted to determine the effect of acute hypoxemia on the collateral circulation.

Methods

Radioactive glass spherules of graded size* coated with Scandium[46] a gamma emitter were introduced into one coronary artery of a beating dog's heart and an attempt was made to recover them from the retrograde flow of what appeared to be an anastomosing artery.[73] Radioactive counting before and after insertion of the spherules established the percentage of beads that crossed the anastomosis to an adjoining arteriole or venule and also which were trapped in the myocardium between the adjoining arterioles (Fig. 1). It was previously determined that the Scandium coating does not diffuse.[52]

Acute coronary ligation. Thirteen mongrel dogs weighing between 20 and 30 kilograms were anesthetized with intravenous pentobarbital sodium (25 mg. per kilogram) and respiration was maintained by a Harvard positive pressure breathing apparatus. Femoral arterial pressure was measured by Statham strain gauge and recorded along with the electrocardiogram on an Electronics for Medicine recorder. Five thousand units of heparin per kilogram of body weight were injected intravenously to prevent coagulation. The chest was opened by a transsternal approach and a branch of the circumflex artery was tied off with a ligature. A polyethylene catheter was inserted and secured into the distal end of the ligated artery and the other end of this catheter connected to a common carotid artery to perfuse the vascular bed supplied by that ligated artery (Fig. 1). An adjoining anterior descending coronary artery which appeared as if it might anastomose directly with the ligated circumflex was cannulated in order to collect all the blood which might pass retrograde across the collateral bed. The retrograde coronary flow was allowed to drip freely into a calibrated tube. The coronary sinus flow was diverted by another cannula so that immediately after injection of the radioactive material all the coronary sinus blood

*Supplied by Minnesota Mining and Manufacturing Company, St. Paul, Minn.

could be collected into a separate beaker

Flow in the carotid artery cannula was interrupted for a few seconds to interpose a length of polyethylene tubing (PE 320) which held 0 5 c c of radioactive spheres suspended in 0 15 per cent Carbopol* (Fig 1) Thus the beads could be flushed into the circumflex artery by a normal pulsating carotid pressure. The retrograde coronary artery and coronary sinus flows were collected simultaneously for five minutes and then the animal was put to death by a lethal dose of Pentothal

The radioactivity of the blood was measured by a well counter After removing the heart radioactive measurements were made of the myocardium and all cannulae by external scintillation counters allowing mathematical corrections for the geometry encountered Knowing the amount of radioactivity before the beads were injected the amount left in the collecting tubes cannulae and myocardium it was possible to calculate the percentage of beads passing across the anastomosis The remainder could always be accounted for because they were trapped in the myocardium between the two arteries.

Chronic coronary ligation Twenty five mongrel dogs were anesthetized with thiopental sodium and under sterile conditions the chest was opened through the left fifth intercostal space A window was incised in the pericardial sac and the anterior descending branch of the left coronary artery was isolated from its bed A ligature was slowly tightened to completely occlude this vessel approximately one centimeter from its origin The pericardial sac was then closed and the chest resutured. The animal was returned to its kennel

Following a predetermined interval of either 3 to 6 or 7 to 12 weeks these animals were anesthetized and the chest reopened by a transsternal incision The coronary collateral circulation was assessed by radioactive spherules by the same methods described above in the acute series

Acute hypoxemia experiments Thirteen animals were prepared in the same fashion as described above for the acute experiments. Hypoxemia was induced by connecting a 100 per cent nitrogen source to the positive pressure respirator Arterial pO_2 was measured before and during the induction of hypoxemia by means of a Beckman Model 100 physiological gas analyzer The average time required to lower the pO_2 to an average of 26 mm. Hg (range 12 to 42 mm Hg) was two minutes. When hypoxemia was induced radioactive beads were perfused into one coronary artery and collected from its anastomosing artery by the method described above

Results

Extent of coronary anastomosis in the normal beating heart In preliminary experiments the largest spherules that passed through anastomotic channels in the normal beating dog s heart were found to be 15 ± 3μ Therefore this size was selected for study

In a group of 13 normal dogs only 0 7 per cent (average) of 15 ± 3μ radioactive beads passed across the circumflex into the adjoining anterior descending coronary artery (Tables I and II) All the remaining beads could be accounted for in the myocardium between these vessels. None of the beads were recovered in the coronary sinus blood

In 12 of the 13 dogs less than 1 per cent of the beads were recovered in the retrograde blood In one dog 1.8 per cent of the beads passed across the anastomosis (Table I)

Extent of anastomosis 21 to 42 days after coronary occlusion In a preliminary series it was noted that both 15 and 35 μ beads crossed equally well between the anastomosing arteries 21 days after occlusion so that 35 μ size was chosen for all subsequent determinations.

In a series of 11 dogs 18 7 per cent of the radioactive spheres 35 μ in size were recovered in the retrograde flow 21 to 42 days following ligation of the anterior descending artery (Table II) All of the remaining beads could be accounted for in the myocardium between the two adjoining arteries.

To estimate the maximum size of anastomotic channels after this time interval 45 μ spherules were perfused into the coronary artery in two other [illegible]ents

*The Carbopol was previously found t be neither sclerosing nor vasospastic

Table I Percentage of radioactivity observed in retrograde blood

Group I *Control group 13 dogs* *Immediately after ligation* *15 ± 5 μ beads* *(Range 0 to 1.8%, average 0.7%)*	*Group II* *11 dogs* *21 to 42 days after ligation* *35 ± 5 μ beads* *(Range 0.5 to 38 4%, average 18.7%)*	*Group III* *11 dogs* *49 to 84 days after ligation* *35 ± 5 μ beads* *(Range 2.7 to 100%, average 40 4%)*
(1) 1 8	(1) 38 4	(1) 100
(2) 0 9	(2) 29 9	(2) 93 6
(3) 0 9	(3) 28 6	(3) 73 0
(4) 0 8	(4) 22 4	(4) 70 3
(5) 0 8	(5) 22 0	(5) 47 0
(6) 0 7	(6) 8 0	(6) 36 0
(7) 0 7	(7) 1 0	(7) 8 2
(8) 0 6	(8) 0 5	(8) 5 5
(9) 0 5	(9) 36 8	(9) 4 5
(10) 0 5	(10) 18 3	(10) 4 0
(11) 0 5	(11) 0 9	(11) 2 7
(12) 0 3		
(13) 0 00		

Table II Summary

Days after ligation of left coronary artery	*Size of radioactive spherules injected*	*Total no of dogs*	*No. of dogs with <1% activity in retrograde blood*	*No. of dogs with >1% activity in retrograde blood*	*Average percentage of radioactivity in retrograde blood*
Control Group I Immediate	15 ± 3 μ	13	12	1	0 7
Group II 21 to 42	35 ± 3 μ	11	2	9	18 7
Group III 49 to 84	35 ± 3 μ	11	0	11	40 4
Group IV Acute hypoxemia	15 ± 3 μ	13	5	8	11 1

20 to 32 days after ligation. Less than 0.5 per cent passed across, indicating the size of the predominant anastomotic channels at the end of this time interval was less than 45 μ.

Extent of anastomosis 49 to 84 days after coronary occlusion. An average of 40 4 per cent of the 35 ± 5 μ spherules were recovered in retrograde flow of the adjoining artery 7 to 12 weeks following the coronary occlusion in 11 animals (Table II) In three of these animals 73 94 and 100 per cent of the beads were recovered in the retrograde blood.

Extent of anastomotic channels during acute hypoxemia. After induction of hypoxemia in 13 dogs with a normal coronary circulation to a mean pO_2 of 28 mm Hg an average of 11 1 per cent of the beads could be recovered in the retrograde flow of the adjoining artery (Tables I and II)

Discussion

There is general agreement that inter coronary anastomotic channels exist after coronary occlusion but difference of opinion continues on whether they are functional in the physiological sense in the normal heart. [8,16,18,22,26,27] Laurie and Woods, using a variety of microdissection techniques at autopsy concluded an extensive coronary anastomosis exists in the normal human heart. Contrary to other investigators that reported a

of sizable anastomotic channels in normal patients than in those with coronary atherosclerosis Prinzmetal and associates[24] and Corday and co-workers[3] injected glass spheres at pressures of up to 200 mm Hg in nonbeating dogs and human hearts at autopsy and reported intercoronary anastomosis of up to 40 μ It is possible that high perfusion pressures used in these studies which exceeded normal diastolic filling pressures were responsible for creating artifactual channels which permitted the spheres to cross the myocardium

Blumgart and his associates[8] and Schlesinger[14] could not demonstrate coronary anastomosis in the pig and human until after coronary occlusion Therefore they concluded that the human and pig must be different than the dog which was alleged to have anastomotic channels of up to 40 μ before occlusion However the contention that the normal dog s heart differs from the human in that regard can not be supported by our studies.

Our experiments performed in the beating dog s heart before and after occlusion delineate the size and extent of interarterial anastomosis under more nearly physiological conditions We realized that the insertion of a catheter in a blood vessel induces some angiospasm Therefore we waited for such a period of time until the retrograde flows appeared near normal as determined by previous studies[2,4,25,26] The uniformity of results obtained in each series of our experiments suggests angiospasm did not influence our observations Heparin was used in all experiments to prevent clotting in the cannulae during the cannulization procedure It was not used at any other time.

In the normal beating dog s heart only an average of 0 7 per cent of the 15 μ beads crossed the anastomosis (Table II) Because beads larger than 15 μ could not pass through it would suggest that the intercoronary anastomosis is less than 15 μ in diameter and is nonfunctional before coronary occlusion.

Three to 6 weeks following ligation 18 7 per cent of 35 μ spheres were found in the retrograde arterial flow This in contrast to the normal dog would appear to be statistically significant ($p < 0\ 001$)[22] suggesting that intercoronary anastomotic channels had developed in response to the chronic ischemia. Very few of the 45 μ spheres could cross at this time, suggesting the luminal diameter of channels was less than 35 μ in caliber Twelve weeks following experimental occlusion 40 per cent of the 35μ beads crossed between the arteries, and in three of these animals, 73 94 and 100 per cent (Table I) Compared to the normal dog this also is statistically significant ($p < 0\ 005$)

These results suggest the coronary arteries of the dog are functionally end arteries before occlusion Twenty-one to 42 days after ligation a significant amount of the beads (18 7 per cent) passed through indicating that these anastomotic channels might sustain myocardial function. However 7 to 12 weeks after occlusion a still more extensive interarterial collateral circulation became activated

Schlesinger[14] came to the conclusion that collateral channels of more than 40 μ in size were present only in arteriosclerotic hearts, and that these channels were functionally significant. His conclusions were made utilizing heavy lead agar in a nonbeating cadaver heart. Our studies in the beating heart would confirm his conclusions

Pathologists demonstrate the area of myocardium in the human is often smaller than that supplied by the occluded artery This suggests some alternative functional circulation must be present because our experiments show the interarterial circulation does not appear significant for 21 days.

If by this study we postulate that an interarterial anastomosis is not functional until 21 days how then can we explain the fact that the infarct is often smaller than the occluded circulation? We believe the infarct size is limited by either a questionable thebesian circulation but more possibly by an overlapping of adjacent arterioles which provide blood to the compromised area[23,24,31]

We proved that hypoxemia could activate the collateral circulation in the normal heart because an average of 11 1 per cent of the 15 μ spheres were recovered in the retrograde circulation of normal dogs hearts. In the same study performed without hypoxemia only 0 7 per cent passed through the anastomotic channels (Table II) This leads us to conclude that coronary arteries are end arteries in a functional

sense prior to occlusion but hypoxemia may induce some interarterial anastomoses.

Summary

1 Experiments using radioactive spherules demonstrate that the coronary interarterial collateral circulation is not functional in the normal dog's heart Hypoxemia can activate some coronary interarterial anastomosis.

2. Three weeks after coronary occlusion the interarterial anastomoses is at least 35 μ in diameter and at 12 weeks is even more extensive.

We are indebted to Willie Davis, Willie Pea, Myles Prevost, and Jeanne Bloom for their technical assistance.

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Case reports

Unusual form of digitalis-induced triple A-V nodal rhythm

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It is well known that digitalis may produce every known type of cardiac arrhythmia resulting from an alteration of impulse formation or conduction although it is an indispensable drug in the treatment of heart failure and most supraventricular tachyarrhythmias. The present paper describes a very unusual form of triple A-V nodal rhythm as a manifestation of digitalis intoxication. The related literature is reviewed.

Case report

A 71-year-old woman suffering from hypertensive and ischemic heart disease was admitted to the Cardiology Service because of increasing dyspnea and fluid retention of one week's duration. Her therapy before admission consisted of digoxin (Lanoxin), 0.25 mg., and hydrochlorothiazide, 50 mg. daily.

The significant findings on physical examination were: blood pressure, 190/105 mm. Hg; irregular pulse at 58 to 95 beats per minute; moderate left ventricular hypertrophy; bilateral basal pulmonary râles; and 2+ ankle edema. X-ray examination of the chest showed moderate left ventricular hypertrophy with pulmonary congestion. The electrocardiogram taken immediately after admission showed an unusual A-V nodal rhythm originating from three different foci (Fig. 1). Blood chemistry was normal, except for a serum potassium of 3.8 mEq. per liter and blood urea nitrogen of 34 mg. per 100 ml. Dilantin (diphenylhydantoin) therapy was instituted in a dose of 125 mg. intravenously. The same dose was repeated four times at 10 minute intervals. Within an hour her cardiac rhythm became less complicated (Fig. 2) and the rhythm progressively improved thereafter.

Analysis of electrocardiogram. In Fig. 1 Leads II-a and b are continuous. Upward directed arrows indicate P waves of sinus origin whereas downward directed arrows indicate ectopic P waves conducted in retrograde fashion (group *A* A-V nodal escape rhythm). In addition, there are two independent A-V nodal tachycardias (indicated by *B* and *C*). The rates of these A-V nodal tachycardias are 78 beats per minute in group *B* and 95 beats per minute in group *C*, respectively. Thus, there is present triple A-V nodal rhythm or tachycardia (groups *A*, *B*, and *C*). It should be noted that occasional ventricular captured beats (marked *CB*) which originate from the group A-V nodal rhythm. In addition, there are present occasional atrial fusion beats which are found between impulses from the sinus node and group *A* nodal pacemaker (marked *FB*). It is interesting that the QRS complexes originating from the group *C* A-V nodal pacemaker show a configuration which differs from the QRS complexes which originate from sinus impulses or group *B* A-V nodal pacemaker. This is due to aberrant ventricular conduction.

In Fig. 2 upward directed arrows indicate sinus P waves whereas downward directed arrows indicate retrograde P waves. This tracing shows double A-V nodal tachycardia (marked *A* and *B*) with occasional ventricular captured beats (marked *CB*) by the sinus node producing incomplete A-V dissociation.

Discussion

The diagnosis of recurrent congestive heart failure was made in this patient. However, it was difficult to judge whether

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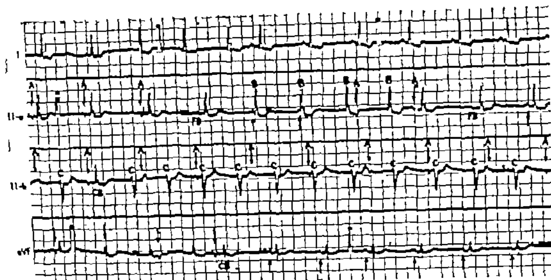


Fig *1* Leads II-a and b are continuous. Upward directed arrows indicate P waves of sinus origin whereas downward directed arrows indicate ectopic P waves conducted in retrograde fashion (group *A* A V nodal rhythm) In addition, there are two independent A V nodal tachycardia (indicated by *B* and *C*). The rates of these A V nodal tachycardias are *78* beats per minute in group *B* and 95 beats per minute in group *C*, respectively This tracing shows triple A V nodal rhythm I addition, there are occasional ventricular captured beats (marked *CB*) and atrial fusion beats (marked *FB*)

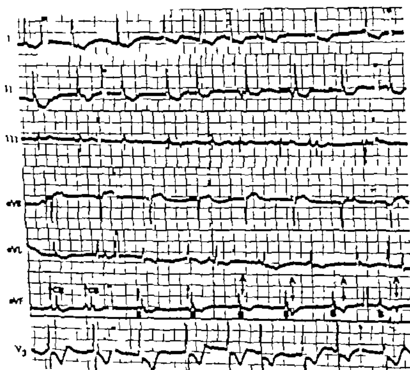


Fig. *2* Upward directed arrows indicate sinus P waves whereas downward directed arrows indicate retrograde P waves. The tracing reveals double A V nodal tachycardia (marked *A* and *B*) with occasional ventricular captured beats by sinus node (marked *CB*) producing incomplete A-V dissociation.

it was a manifestation of digitalis intoxication clinically. Digitalis toxicity was suspected because she was an elderly patient who had been taking diuretics along with digoxin and A V nodal rhythm or nonparoxysmal A V nodal tachycardia particularly that which is multifocal in origin is known to be associated with such a situation.[1-4]

It is well documented that digitalis frequently induces various A V nodal arrhythmias either due to passive impulse formation resulting in A V nodal escape rhythm as a physiologic mechanism or enhancement of A V nodal impulse formation resulting in A V nodal tachycardia.[1-4] The incidence of digitalis-induced A V nodal arrhythmias has increased markedly in recent years probably because of a better understanding regarding the arrhythmia itself and a common association of atrial fibrillation as an underlying rhythm.[1,3]

The importance of recognizing A V dissociation is well known because A V nodal arrhythmias almost always are associated with A V dissociation.[1-4] By definition A V dissociation indicates that the atria and ventricles beat independently resulting in P wave and QRS complexes lacking a constant relationship on the electrocardiogram.[5,6] In a rare form of A V dissociation the atria and ventricles may be controlled by two different pacemakers at the A V junction[7] as seen in Figs. 1 and 2. In this circumstance the atria are activated in retrograde fashion. Occasionally the atria may be intermittently activated by the sinus node in the presence of double or triple A V nodal rhythm (or tachycardia) resulting in triple (Fig. 2) or quadriple rhythms (Fig. 1). In this case atrial fusion beats between antegrade sinus impulses and retrograde A V nodal impulses may occur as seen in Fig. 1. Each pacemaker at the A V junction may produce an A V nodal escape rhythm or nonparoxysmal A V nodal tachycardia but in the majority of the reported cases in the literature double A V nodal rhythm or tachycardia from the lower A V nodal pacemaker induced a more rapid rate than the upper pacemaker.[7] Captured beats (partial or complete, atrial or ventricular) may occur if there is no complete A V block (either forward or retrograde). In a previous study of double A V nodal rhythm[7] four out of five cases had unequivocal digitalis intoxication so that the presence of this rare arrhythmia is almost a pathognomonic sign of digitalis toxicity during digitalis therapy. For a similar reason the appearance of triple A V nodal rhythm or tachycardia during digitalization may indicate a more pathognomonic sign of digitalis intoxication. The occurrence of triple A V nodal rhythm due to digitalis toxicity has not previously been reported in so far as this author can ascertain. In one case,[8] the rare combination of double supraventricular (atrial and A V nodal) tachycardia associated with parasystolic ventricular tachycardia producing a triple tachycardia was noted by this author.

In elderly patients, such as herein reported who are being treated for congestive heart failure with digitalis and diuretics digitalis intoxication may be easily produced since such patients have poor myocardial reserve and are especially sensitive to digitalis. The sudden appearance of complex arrhythmias, particularly those A V nodal in origin during digitalization in elderly individuals should make one suspicious of digitalis toxicity rather than the need for increased digitalis.

Summary

An instance of digitalis-induced triple A V nodal rhythm has been described. To my knowledge, it is the first arrhythmia reported.

The necessity of early recognition of digitalis intoxication in elderly patients who develop A V nodal arrhythmias particularly those multifocal in origin during digitalization has been emphasized.

I wish to express my sincere appreciation to Mrs. Carol Johnson for her valuable secretarial assistance in the preparation of this manuscript.

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before death) the ECG was repeated. It was again normal, and there was no significant change from the previous tracing.

Autopsy revealed a mesomorphic male, measuring 69 inches in length, and estimated to weigh 185 pounds. Except for skin lesions on the heels (see comments below), the significant findings at autopsy were limited to the heart and lungs. Moderate cardiac hypertrophy was present, the heart weighing 460 grams. The right ventricle measured 5 mm. and the left ventricle measured 20 mm. in thickness. Several of the mitral chordae tendineae were thickened and fused, but there was no anatomic evidence of functional impairment, and no other evidence of rheumatic disease. The muscular myocardium was not grossly infarcted.



Fig. 1. Close-up gross photograph of aortic valve, showing oblique origin of left coronary artery (probe) adjacent to ostium of right coronary artery.

The right coronary artery originated normally behind the right aortic cusp, and was very long vessel which branched into the posterior descending artery and continued toward the lateral wall of the left ventricle where it supplied muscle normally serviced by the circumflex branch of the left coronary artery. Arteriosclerosis of severe degree was present, the right coronary artery showing focal areas of 90 per cent attenuation.

The left coronary artery arose independently also behind the right aortic cusp (synonyms are anterior, right anterior, right adjacent[4]) and just to the left of the right orifice (Fig. 1). It turned obliquely towards the left, and passed between the bases of the aorta and pulmonary artery (Fig. 2). It then descended in the anterior longitudinal sulcus on the anterior surface of the heart, but there was no circumflex branch. This vessel showed 10 per cent attenuation of its lumen due to arteriosclerosis. Prior to arteriosclerosis, the right and left coronary arteries had been equal in diameter.

Microscopic examination of randomly selected sections of heart muscle revealed no tissue changes suggestive of infarction. The lungs, which weighed 510 and 470 grams, right and left respectively, showed slight congestion and moderate emphysema of the diffuse type. A cross section of the left coronary artery at the level of its passage between the aorta and pulmonary artery revealed a normal-sized vessel with some arteriosclerotic changes (Fig. 3).

Discussion

Possible electrical burns on the heels (the electric razor) were attributed after further

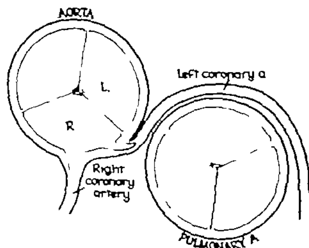


Fig. 2. Diagram of anomaly of left coronary artery with origin from right aortic sinus, and course between bases of aorta and pulmonary artery. N circumflex branch.

Anomalous aortic origin of coronary artery with sudden death Case report and review

Peter A Benson M.D
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When both the right and left coronary arteries originate from the aorta the actual site of origin has been considered to be of little consequence since the coronary blood will be fully oxygenated[1] There appears to be an entity not previously recognized in which the left coronary artery has an anomalous aortic origin from the right sinus of Valsalva its subsequent course takes it between the great arterial trunks at the base of the heart where it is subjected to a squeezing action with resulting coronary insufficiency and sudden death

The present case is an unusual example of this condition which has been described as case reports in only four previous instances.[2-4] Two of the four previous cases were reported by the author[4] and the addition of the present case to this series suggests that this anomaly may be more prevalent than heretofore recognized and constitutes an entity with fatal potential In none of the cases was a coronary artery anomaly suspected before autopsy

Case report

A 54-year-old Caucasian warehouseman was shaving with an electric razor when he cried out his wife's name. She ran to the bathroom where she found him kneeling on the floor clutching his chest, and moaning With no more words he fell to the floor Resuscitation attempts were unsuccessful. An ambulance took him to the hospital where he was pronounced dead on arrival.

During the 3 months before his death he had suffered chest pains, and had been seen as an out patient on five occasions. The first visit (57 days before death) was to the emergency room where he described epigastric "gas pains" or *substernal* "burning" with radiation to his neck which he had first noticed 3 weeks before These pains were episodic, occurring irregularly and sometimes at night they were often accompanied by cold sweats. He denied shortness of breath Blood pressure was 137/70 mm Hg and the radial pulse rate was 80 per minute and regular The initial impression was esophagitis and he was given antacids, but a clinic appointment was made to permit further studies to rule out angina pectoris.

On his second visit (50 days before death) he again complained of chest pain which he now said increased with exertion, but decreased with elevation of his arms above his head. Blood pressure was 155/85 mm Hg and pulse 80. Laboratory results were as follows serum glutamic oxaloacetic transaminase (SGOT) was 25 Babson U (normal 10 to 32) lactic dehydrogenase (LDH) was 46 U (normal 24 to 78) the white blood count was 8,500 per cu. mm with 65 neutrophils 34 lymphocytes, and 1 monocyte. The hematocrit was 44 and the erythrocyte sedimentation rate (ESR) was 18 mm. per hour (Westergren) Serum cholesterol was 222 mg per 100 ml An electrocardiogram (ECG) taken this day was read as normal with a heart rate of 65 beat per minute.

On his third visit (43 days before death) his chest pains were noted to be less frequent and not as severe. The pains were not relieved by nitroglycerin His fourth visit (36 days before death) was notated Continuing substernal burning with radiation to the sternal notch On his fifth and last visit (29 days

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unusual oblique origin of the anomalous vessel.

Coronary malformations of any type are rare. The particular anomaly presented here is not recognized in the textbooks as a potentially lethal malformation. Origin of coronary arteries from the pulmonary artery is a well-known entity.[1] Single coronary arteries which subsequently branch into right and left arteries have been described a few times,[2,3] and in several of these cases the anomalous vessel passed briefly through the heart muscle and may have passed between the aorta and pulmonary artery. The causes of death, however, were not related to the heart. The five cases presented and reviewed here indicate that this particular anomalous aortic origin of the left coronary artery is *not innocuous*. Hopefully, the recognition of this anomaly will lead to effective methods for its diagnosis and treatment.

Summary

This case report describes an anomalous origin of the left coronary artery. Despite the origin of the vessel from the aorta, this anomaly results in sudden death from coronary insufficiency because of the unusual course of the vessel between the aorta and pulmonary artery. This coronary artery anomaly has been described four times before in case reports, but it is not generally recognized as an entity with fatal potential.

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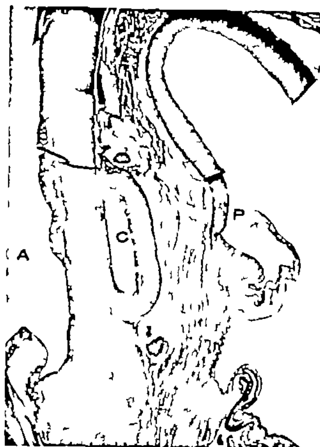


Fig 3 Cross section of left coronary artery near its origin showing its position between aorta and pulmonary artery There is some separation due to tissue preparation *A* Aorta *P* pulmonary artery *C* coronary artery (Hematoxylin and eosin × 7)

investigation to the effects of postmortem contact with a heating register

The anomalous origin and course of the left coronary artery in the present case is very similar to those of the four previously reported cases. In each case the artery originated in an oblique manner very close to the normal ostium of the right coronary artery and then passed between the great arterial trunks at the base of the heart. The present case is unusual because the age at the time of death was far greater than that reported in previous cases 11 to 14 years. The case described by Jokl and associates[2] was that of a boy aged 14 who died suddenly after completion of a two mile race His heart weighed 350 grams and the left ventricle was hypertrophied The right and left coronary arteries originated close to each other from a common funnel or outpouching of the right aortic sinus. The left coronary artery was only half as large as the right. The authors explanation for the coronary insufficiency was a peculiar syphon like kink as well as the small size of the vessel and death was ascribed to ventricular fibrillation

The case of Cohen and associates[3] was that of an 11 year-old boy who suffered a myocardial infarct following a short run. He survived 19 hours in the hospital and clinical confirmation of the infarct was obtained Autopsy revealed a heart weighing 280 grams. The left coronary artery arose behind the anterior cusp immediately to the left of the right coronary ostium. It turned sharply to the left passed between the aorta and pulmonary artery and branched as usual into the circumflex artery The course of the vessel and the sharp angulation at the origin were believed to explain the coronary insufficiency with infarction

Case No 1 of Benson and Lack[4] was a 13 year-old Caucasian boy who died suddenly following a running chase The heart weighed 260 grams The origin and course of the left coronary artery was identical to that described by Cohen Case No 2 was a 13 year-old Negro boy who died shortly after collapsing during a basketball game The heart weighed 370 grams and was hypertrophied In this case, the left coronary artery originated independently from the right coronary artery behind the right aortic sinus but as in Jokl s case an outpouching of the aorta at this site formed a slight funnel like configuration The left coronary artery turned sharply to the left and passed between the aorta and pulmonary artery The left anterior descending artery was small and the circumflex branch was very small

All five cases were males with unsuspected anomalous aortic origin of the left coronary artery In the four previous cases, the left coronary artery was described as smaller than the right Some degree of cardiac hypertrophy was present in all cases. It is interesting that the present case showed much less arteriosclerosis in the left coronary artery than in the right, suggesting that the anatomic arrangement resulted in less hemodynamic stress. It is a presumption that it is the position of the vessel between the aorta and pulmonary artery that permits a squeezing action an alternate explanation might include the

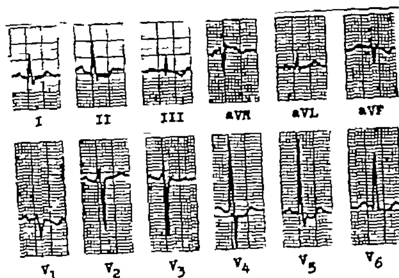


Fig. 1 The electrocardiogram.



Fig. 2. Roentgenograms of thorax. Frontal view b, Lateral view

(Fig. 3) Pulmonary function tests showed no expiratory slowing. The vital capacity and maximum breathing capacity were 76 per cent and 75 per cent of their predicted values, respectively. The values did not change after using bronchodilators. The usual tests upon the blood and urine gave negative results.

The results of the cardiac catheterization are summarized in Table I and the pulmonary arterial "wedge" pressure is reproduced in Fig. 4.

Indicator dilution curves made by injection of Cardio-Green dye into the pulmonary artery revealed a low peak concentration and marked prolongation of the disappearance slope. In the absence of cardiac shunts, the curves suggest valvular insufficiency.

Dr. Johnson, will you present the findings of left ventriculography?

DR. THOMAS JOHNSON: Left ventriculography was performed by retrograde passage of the catheter from the aorta into the left

Clinical pathologic conference

Kyung Soon Lee M.D
Thomas Johnson M.D
James N Karnegis M.D
Frank W Quattlebaum M D
*Jesse E Edwards M.D **
St Paul Minn

DR KYUNG SOON LEE A 70-year-old man was admitted because of shortness of breath He had a ten year history of asthma manifested by a feeling of tightness in the chest and shortness of breath For the last two years symptomatic relief resulted from administration of theophylline ephedrine and phenobarbital as needed.

Two months before admission the patient noticed an increasingly severe feeling of tightness in the chest together with shortness of breath He also felt some thoracic discomfort Although he could not further describe the abnormal feeling in the chest, he stated that he had never felt a similar sensation with any asthma attack.

There was no family history of cardiovascular diseases or symptoms. One sister also suffered from asthma The remainder of the history was not remarkable

Physical examination by his physician showed cardiomegaly and râles were heard over both lungs. A cardiac murmur had never been heard on frequent examinations in the past but a loud systolic murmur was now present.

Treatment included digitalis, diuretics and restriction of salt. The symptoms markedly improved and the cardiac size as observed in thoracic roentgenograms became slightly reduced

The patient was referred for further evaluation Physical examination showed the blood pressure to be 124/80 mm Hg Positive findings were limited to the heart. The cardiac rhythm was regular There was left ventricular enlargement to palpation and a systolic thrill at the apex. The first cardiac sound was normal and was followed by a Grade 5/6 pansystolic murmur at the apex. The murmur radiated well toward the left axilla and to a lesser extent upward along the left sternal border A third cardiac sound was present. No diastolic murmur was heard The lungs were clear the liver was not palpable and there was no peripheral edema

The electrocardiogram (Fig 1) showed normal sinus rhythm and slight sagging of the S-T segments.

Thoracic roentgenograms revealed moderately severe left ventricular enlargement and signs of extensive central pulmonary vascular congestion (Fig 2) The cardiac size was increased compared to that of studies done about six months earlier

Cardiac fluoroscopy showed left ventricular enlargement The enlarged left atrium displaced the esophagus posteriorly

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Reprint requests to Jesse E. Edwards, M.D., Pathology Department, Charles T Miller Hospital, 125 West College Ave., St. Paul, Minn. 55102.



Fig. 5 Left entriculograms in frontal ( ) and lateral (b) views.

normal sinus rhythm a diphasic P wave in Lead V_1 and nonspecific ST T changes consistent with digitalis effect.

Cardiac catheterization excluded a left to-right shunt and confirmed the presence of mitral insufficiency (Table I) The results indicated hemodynamic left ventricular decompensation The pulmonary arterial wedge pressure showed a huge cv' wave, resulting from severe mitral reflux. The mean wedge pressure was at pulmonary edema level and the pulmonary arterial pressure was elevated. The cardiac index was low and this accounts for the pulmonary arterial blood oxygen desaturation.

The left ventriculogram demonstrated severe mitral insufficiency The left ventricle and left atrium were only mildly enlarged. Left ventricular contractions were good

Several features help to differentiate mitral insufficiency caused by sudden loss of valvular support from the more usual rheumatic variety Ruptured chordae or papillary muscle is suggested by the sudden onset of mitral insufficiency and a short duration of the condition which is clinically not well tolerated. The cardiac rhythm tends to be of sinus type and a loud third or fourth heart sound may be present. The size of the heart, in general and the left atrium in particular are often surprisingly small considering the severity of the mitral insufficiency The wedge pressure usually shows huge regurgitant cv waves. There is no evidence of mitral stenosis and usually none of aortic valvular disease.

In contrast, patients with rheumatic mitral insufficiency may have a history of rheumatic fever and of mitral insufficiency of long duration. Evidence of coexistent mitral stenosis or aortic valvular disease may be present. The lesion is better tolerated and the clinical course more benign than is the case with mitral insufficiency resulting from loss of support of valvular tissue. The cardiac rhythm is often atrial fibrillation. The heart tends to be larger as does the left atrium. The wedge pressure, although elevated does not usually show huge spiking cv" waves, probably as a result of the fact that the large left atrium has lost much of its distensibility

Chordal rupture may be spontaneous or may follow trauma or bacterial endocarditis. A papillary muscle may rupture as part of the damage caused by myocardial infarction or following trauma. Rupture of the posterior papillary muscle is more common than that of the anterior papillary muscle. It is often difficult to decide preoperatively whether the patient has ruptured chordae or papillary muscle, since



Fig 3 Esophagram in lateral view showing evidence of posterior displacement of esophagus by enlargement of the left atrium

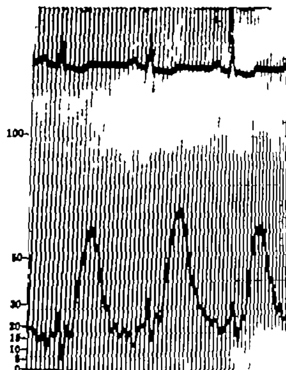


Fig 4 Pulmonary arterial wedge pressure pulse (below). Numbers indicate pressure in millimeters of mercury Electrocardiogram above.

Table I Synopsis of cardiac catheterization data

Site	Pressure (mm Hg)	Blood oxygen saturation (per cent)
Right atrium	a8 v9 mean 5	60
Right ventricle	70/0, 6	—
Pulmonary artery	75/23 mean 46	59
Pulmonary arterial wedge	cv75 mean 35	—
Brachial artery	118/70 mean 87	96
Left ventricle	117/0 20	—

The cardiac index was 2.1 L./min./M².

ventricle (Fig 5) This demonstrated mitral insufficiency of 4+ severity associated with distension of the left atrium and the central pulmonary veins with each ventricular contraction The left atrium and ventricle were only moderately enlarged and the left ventricular contraction was of good quality

DR LEE Dr Karnegis, will you discuss the differential diagnosis?

DR. JAMES N KARNEGIS The patient had a history of chronic pulmonary disease but two weeks before admission had a new and acute disorder For the first time he had a sort of discomfort in his chest and was found to have acute congestive cardiac failure.

Coupled with the sudden onset of cardiac failure was the definite finding of a new murmur This fact is of great diagnostic importance and brings to mind two conditions, namely acute mitral insufficiency and acute ventricular septal defect.

Acute mitral insufficiency may result from the loss of supporting structures, such as from rupture either of chordae tendineae or of a papillary muscle Each condition presents clinically as acute mitral insufficiency Other causes of mitral insufficiency such as rheumatic mitral valvulitis trauma and infection seem unlikely in this setting

The physical examination suggested mitral insufficiency rather than a ventricular septal defect. This was further supported by the cardiac fluoroscopy which showed left atrial and left ventricular enlargement and central pulmonary congestion The findings in the electrocardiogram included

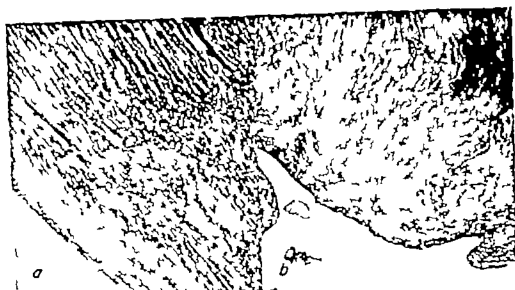


Fig. 7. Photomicrographs of one of the fragments of papillary muscle attached to the mitral valve shown in Fig. 6. a, Junction of infarcted myocardial tissue (above) and the zone of reaction (below). (Hematoxylin and eosin. × 45.) b, Lowermost portion of fragment of muscle removed. The necrotic muscle has been removed entirely and replaced by dense fibrous tissue. An endothelial lining covers the lower portion of the specimen which represents the site of rupture. (Hematoxylin and eosin × 60.)

follow-up study one month later the patient reported that he was in good health.

DR. LEE: Dr. Edwards will present the pathologic findings and make some closing remarks.

DR. JESSE E. EDWARDS: The specimen consisted of several pieces of mitral valve which in aggregate linear dimension, measured 5 cm. The chordae, as well as the valvular tissue, were delicate. To two of the pieces of valvular tissue, papillary muscle fragments were attached by chordae. Each piece of papillary muscle was conical in shape and measured about 1 cm. from above and downward and about 8 mm. in width at the base (Fig. 6). The tissue was of abnormal color varying from gray to brown. The lower extremity of each fragment of papillary muscle was undulated and shiny as though covered by endothelium.

Histologic examination showed that, in each papillary muscle, there was a central zone of infarcted cardiac muscle surrounded by a reactive process (Fig. 7).

Immediately around the residual muscle, there were numerous fibroblasts and macrophages. Many of the latter contained pigment. Most distally peripherally and including the rupture site connective tissue of avascular nature was present. Endothelium covered the connective tissue at the site of rupture. The chordae tendineae and leaflet tissue of the valve were not remarkable.

This case is an example of an uncommon type of rupture of the heart as a complication of acute myocardial infarction, the other two types being rupture of the free wall of the left ventricle and rupture of the ventricular septum.

Pathologic experience indicates that one or another form of rupture of the heart is a cause of death in about 15 per cent of all fatal cases of acute myocardial infarction. Of these about 85 per cent are represented by rupture of the free wall of the left ventricle with resulting hemopericardium. (An undetermined but small percentage of cases with rupture of the free wall survive to develop false aneurysms of the left ventricle.)

About 10 per cent of fatal cases of rupture of the heart are examples of rupture of the ventricular septum. The resulting left-to-right shunt is usually responsible for death shortly after the event of rupture although in isolated cases survival for months or years may occur.

The least common type of rupture com

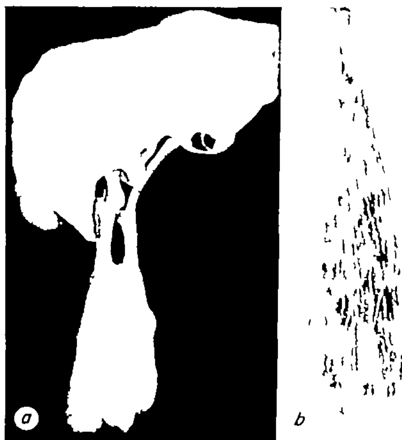


Fig 6 a Gross view of a portion of the mitral valve and one of the two fragments of ruptured papillary muscle The lower end of the muscle (rupture site) is lobulated and covered by a shiny surface b Low power photomicrograph of the papillary muscle. The central part contains necrotic muscle. The periphery shows reactive tissue (Hematoxylin and eosin. × 3 8.)

the two different anatomic states yield identical hemodynamic disturbances

In the case presented the electrocardiogram did not show changes diagnostic of myocardial infarction a factor suggesting that a papillary muscle was not involved Also chordal rupture tends to cause lesser degrees of mitral insufficiency than rupture of a papillary muscle Usually the latter results in fulminating mitral insufficiency and a precipitous clinical deterioration On that basis, chordal rupture might be favored in this patient but rupture of a papillary muscle is a possibility that cannot be excluded In either situation surgical correction seems indicated

DR LEE The patient was operated upon and I shall ask Dr Quattlebaum to present the operative findings.

DR. FRANK W QUATTLEBAUM On March 13 1969 under conditions of total cardiopulmonary bypass and hypothermia (29° C) ventricular fibrillation was induced From the opened left atrium it was apparent that the mitral valve was flail a feature resulting from rupture of part of the posteromedial group of papillary muscles. Two small segments of papillary muscle attached to chordae were lying free in the left ventricular cavity The mitral chordae and leaflets were delicate and thin The mitral valve was removed and replaced by a Starr Edwards mitral valvular prosthesis

Several days postoperatively respiratory distress appeared It was associated with wheezing and difficulty in bringing up secretions On the thirteenth postoperative day cardiac arrest occurred and responded promptly to external cardiac massage. On the same day tracheostomy was performed which resulted in improvement of the respiratory problem The tube was removed two weeks later as general improvement became apparent

The patient was discharged in an ambulatory state on April 20 1969 approximately five weeks after operation In a

Hyperthyroidism as a high cardiac output state

W J deGroot M.D
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Hyperthyroidism has been of interest as a cardiovascular disorder since it was first described more than a century ago. Indeed its earliest recognition was as a circulatory disease. The swollen vascular goiter was thought by early observers to represent the result of and not the cause of the hyperdynamic circulation.

Clinical Graves disease is one of the disorders commonly classified under the heading of high output failure but more appropriately termed hyperkinetic circulatory states. Although all of the hyperkinetic circulatory states have certain features in common, they each have other characteristics which make them distinctive. This is particularly true of hyperthyroidism. All of the high cardiac output states listed in Table I are associated with a low peripheral resistance, but in each the location of the low resistant circuit is unique and the distribution of organ blood flow different. An interesting and perhaps important example when one speculates on the genesis of heart failure in these diseases, is the blood flow to the kidney In most patients with chronic severe anemia,[10,11] long-standing arteriovenous fistula and beriberi,[7,11] and in exercising normal man,[11] the renal blood flow is decreased. In A V fistulas of short duration renal blood flow is normal[11] and in hyperthyroid patients renal blood flow is normal or slightly increased.[11, 5] Thus it would appear that in most hyperkinetic circulatory syndromes blood is shunted from the kidneys to supply the low resistance circuit while in hyperthyroidism renal perfusion neither limits nor contributes to the high cardiac output.

It can also be noted from Table I that in thyrotoxicosis and exercise there is an increased oxygen consumption associated with a high cardiac output. This would suggest that the increased cardiac output of hyperthyroidism, like that of exercise is determined by increased metabolic needs. This mechanism may be operative to some degree, but it certainly does not explain the profound acceleration of flow seen in thyrotoxicosis. In hyperthyroidism the augmentation of cardiac output when compared to oxygen utilization is far in excess of that observed during exercise (Fig 1) Indeed when viewed from this perspective, hyperthyroidism appears to demonstrate a considerably more striking circulatory derangement than metabolic one.

Increased oxygen consumption to the level observed in thyrotoxicosis in all probability does not require any change in cardiac output. Aspirin administration to volunteers in quantities sufficient to raise

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plicating myocardial infarction is that represented by the case herein presented namely rupture of a papillary muscle In the classical example of rupture of a papillary muscle the myocardial infarct lies in a posterolateral position and the posteromedial papillary muscle ruptures The usual phenomenon is that death with pulmonary edema occurs shortly after the event of rupture. The basis for early death is that rupture usually involves the entire papillary muscle and the resulting mitral insufficiency is massive.

Only a few cases of myocardial infarction with rupture of a papillary muscle with survival for months have been reported (Fischer[2] 10 months Breneman and Drake[3] 14 and 5 months, respectively) In these cases as in that of Austen and associates[4] and in our case it appeared that certain elements of a papillary muscle complex had ruptured

Experience with surgical treatment of rupture of a papillary muscle of the left ventricle following myocardial infarction is limited As far as we are aware the first case treated surgically was the patient of Austen and associates. In their case the rupture involved the anterolateral papillary muscle.

Prosthetic replacement of the mitral valve was performed about 2½ months after the event of rupture. The postoperative course was successful To our knowledge the operation performed by Dr Quattlebaum on the case described represents the second case treated as in Austen s case

The rarity of chronic mitral insufficiency resulting from rupture of a papillary muscle should not obscure the fact that infarction of papillary muscles, especially the posteromedial one is a very common phenomenon in classical myocardial infarction While this infarcted papillary muscle does not often rupture function of the nonruptured infarcted muscle may be faulty[5]

We have observed an example of acutely arising massive mitral insufficiency in case of acute posterior myocardial infarction with involvement of the related papillary muscle which had not ruptured More commonly infarction with scarring of a papillary muscle may be associated with varying degrees of mitral insufficiency in patients who have recovered from acute myocardial infarction

Final diagnosis

The final diagnosis is acute myocardial infarction with long term survival following papillary muscular rupture

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Fundamentals of clinical cardiology

Hyperthyroidism as a high cardiac output state

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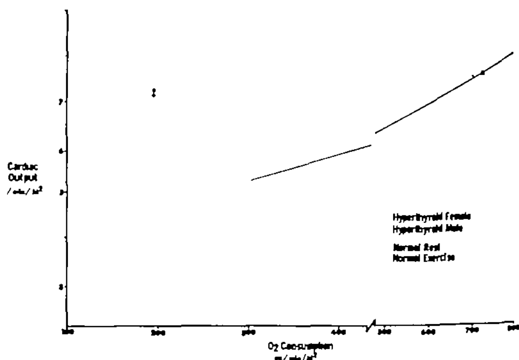


Fig 1 Relationship between oxygen consumption and cardiac output. Patients with thyrotoxicosis are compared with a group of normal men at rest and during moderately severe exercise Solid line depicts regression equation from Donald and associates[8] for normal exercising males.

*Table I Common high cardiac output states**

State	*Oxygen consumption* (%)	*Cardiac output* (%)	*Heart rate* (%)	*Peripheral resistance* (%)
Anemia	Normal	↑ 65	↑ 35	↓ 30
A V fistula	Normal	↑ 125	↑ 55	↓ 45
Beriberi	↑ 10	↑ 170	↑ 50	↓ 55
Exercise	↑ 300	↑ 100	↑ 70	↓ 35
Hyperthyroidism	↑ 45	↑ 100	↑ 60	↓ 35

*Percentages are gross approximations derived from the references cited (see text)

the metabolic rate to levels comparable to that seen in clinical thyrotoxicosis does not substantially change the cardiac output (Fig 2).[17] Perhaps more significantly dinitrophenol given to animals does not change the cardiac output until oxygen utilization is well above twice the control level.[18] When dinitrophenol is given in amounts sufficient to increase oxygen consumption 400 to 500 per cent and body temperatures 3 to 5° F above control levels cardiac output increases a relatively modest 100 per cent.[19] Not only does this data tend to emphasize the dicotomy between the circulatory and metabolic effects of hypermetabolic states but it also casts some doubt on the argument that the high cardiac output of thyrotoxicosis is required to dissipate excess body heat. At least excess heat generation does not appear to be an obligatory mechanism in the production of a high cardiac output. The circulatory and metabolic consequences of dinitrophenol administration to the intact animal are particularly interesting since both dinitrophenol and thyroid hormone increase oxygen utilization by altering mitochondrial metabolism. In vitro studies have shown that both agents can alter mitochondrial structure and function.[20,21]

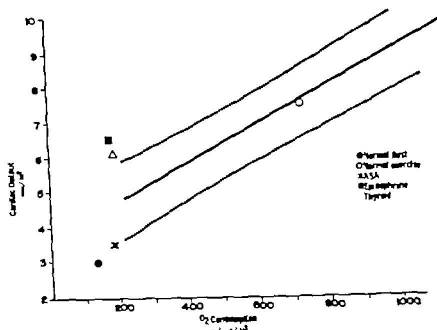


Fig. 2. Relationship of cardiac output and oxygen consumption in four hypermetabolic states. Solid and dotted lines represent regression line and 95 per cent confidence limits for normal exercising males (Donald and associates[illegible]).

The metabolic and circulatory changes observed in hyperthyroidism are quite similar to those observed in normal volunteers during epinephrine infusion (Fig. 2). This would suggest that the circulatory manifestations of thyrotoxicosis are mediated through the sympatho-adreno-medullary system. Such a mechanism has been postulated on the basis of some animal studies and certain clinical observations.[illegible] However, recent detailed hemodynamic studies have failed to substantiate this hypothesis. Reserpine induced catecholamine depletion does not significantly alter the oxygen consumption or cardiac output of thyrotoxic patients (Fig. 3).[illegible] Nor have alterations in cardiac output been produced by beta-adrenergic blocking agents or by the oral administration of large doses of guanethidine.[illegible] The parenteral administration of guanethidine for 24 to 48 hours has been reported to lower cardiac output in some patients but not to normal levels.[illegible]

These studies have essentially excluded the sympathetic neurotransmitters as significant mediators of thyroid hormone activity. This important concept has been substantiated by in vitro observations. Thyroid possesses strong positive chronotropic properties even in the absence of autonomic innervation.[illegible] In addition, myocardial force velocity relationships which are dramatically altered by thyroid are essentially the same before and after catecholamine depletion.[illegible]

It is now apparent that the bulk of recent evidence strongly supports the concept that a high cardiac output is an intrinsic manifestation of thyroid hormone excess and that the sympathetic nervous system is not essential in the genesis of the hyperkinetic circulatory state. There is no doubt, however, that the autonomic nervous system in hyperthyroidism modulates the cardiac response to stress much the same as it does in normal individuals.

Although the exact mechanism by which thyroid hormone induces a high cardiac output remains obscure, recent evidence has emphasized the important regulatory role of peripheral vascular resistance. Administration of the selective alpha adrenergic stimulant, phenylephrine, to a group of atropinized thyrotoxic patients reduced the cardiac output to a level

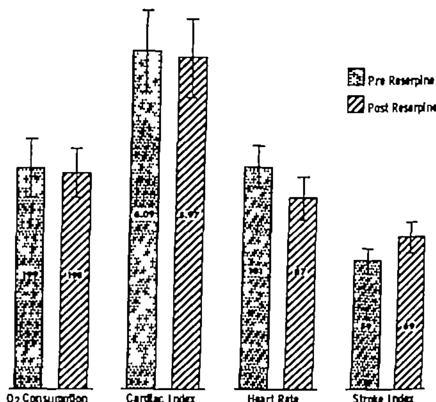


Fig 3 Metabolic and hemodynamic changes observed in hyperthyroid patients before and after parenteral reserpine administration.

somewhat below a comparably treated euthyroid group[22] It would appear from these data that the cardiac response in hyperthyroidism is entirely secondary to peripheral circulatory demands. This interpretation would require modification to include the direct cardiac effect of thyroid hormone The positive chronotropic and inotropic properties of thyroid have been well documented[19,31]

Hemodynamics

The cardiac output is increased in almost all patients with hyperthyroidism This is true even in those patients who have basal oxygen consumptions which are not outside the range of normal (Fig 1) While the changes in cardiac output appear to bear a close correlation with the changes in oxygen utilization it has become increasingly evident that these alterations are two independent manifestations of thyrotoxicosis. This view is strengthened by the observation that phenylephrine infusion can normalize the cardiac output in thyrotoxic patients presumably without changing the oxygen consumption.[22]

As previously stated regional distribution of blood flow in hyperthyroidism is not uniform Cerebral and hepatic blood flows are normal[23,24] Renal blood flow is normal or only slightly increased[23,16] The coronary blood flow is increased approximately 60 per cent above normal and myocardial oxygen utilization is increased a comparable amount.[25] Much or all of the increased coronary flow and increased myocardial energy utilization is expended by the thyrotoxic heart in delivering the accelerated cardiac output. Skeletal muscle blood flow is substantially increased[26] Increased muscle oxygen utilization induced by uncoupled mitochondrial oxidative phosphorylation was previously thought to offer adequate reason for this high flow This explanation is not entirely consonant with present information While muscle mitochondrial oxygen uptake is increased in hyperthyroidism oxidative phosphorylation is tightly coupled[27] In addition studies of hepatic flow have shown that increased oxygen utilization does not in itself cause increased flow[24] Skin blood flow is increased more than 200 per cent above euthyroid control values.[11,27] This extremely high skin flow can explain

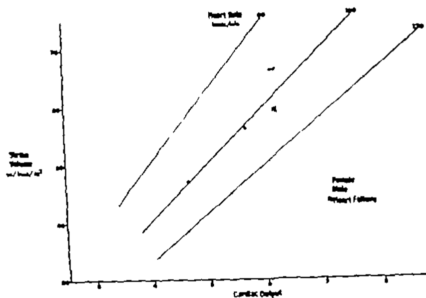


Fig. 4. Cardiac output, heart rate, and stroke volume relationships in 39 untreated hyperthyroid patients.

much of the high cardiac output of thyrotoxicosis. It also provides one of the major arguments that the accelerated cardiac output of hyperthyroidism is required to dissipate excess metabolic heat.

The delivery of a high cardiac output by the thyrotoxic heart is accomplished by a group of interrelated mechanisms. The heart rate is accelerated in most patients. There is frequently an augmentation of stroke volume and myocardial contractility is invariably enhanced.

Although the heart rate is increased in most patients with thyrotoxicosis, the degree of tachycardia bears no relationship with the level of cardiac output. Heart rates of 100 beats per minute have been observed in patients with only slightly increased cardiac outputs as well as in patients with cardiac outputs as high as 6.0 L. per minute per square meter (Fig. 4). When the disease induces modest elevations of cardiac output it is usually delivered almost entirely by cardioacceleration. As the demands for flow are increased there is progressive augmentation of stroke volume. The relationship of stroke volume to cardiac output is reasonably linear (Fig. 4). When the cardiac output is excessively high (in the range of 6.5 L. per minute per square meter or higher) the increased cardiac output is supplied as much by an increased stroke volume as by an accelerated heart rate. While it is not known whether the heart produces the increased stroke volume by increasing systolic emptying from a normal diastolic volume or by increasing end-diastolic volume, it is probable that both mechanisms are operative. There is reasonable clinical evidence that diastolic volume is increased in some patients.[38]

The duration of left ventricular systole is substantially shortened in hyperthyroid patients. The pre-ejection phase of systole is decreased approximately 40 per cent when compared to euthyroid controls. The ejection phase is not only abbreviated when compared to euthyroid patients with slow heart rates, but when correction factors are employed to compensate for the fast heart rate, ejection time is still inordinately fast.[39] This is particularly interesting in view of the fact that stroke volume, which is increased in many of these patients, ordinarily lengthens the ejection time. This strongly suggests that the force of left ventricular ejection is increased more than would be anticipated by the Frank-Starling mechanism and that myocardial contractility is increased. The changes in the contractile state of the thyrotoxic myocardium are not influenced by catecholamine stores. Reserpine administration does

not significantly change the duration of the pre-ejection or ejection phases of left ventricular systole although it does slow the pulse and cause further augmentation of stroke volume.

Studies performed on the isolated cat papillary muscle have further characterized the influence of thyroid hormone on the contractile properties of the heart.[31] Hyperthyroidism accelerates the rate of isometric tension development and shortens the time to peak tension without significantly changing peak tension It also increases the velocity of isotonic shortening These changes are essentially the same whether or not the papillary muscle is depleted of catecholamines.

The combination of a shortened ejection time and a substantially increased stroke volume markedly accelerates the rate with which blood is ejected from the ventricle[29] While the mean rate of left ventricular ejection in normal individuals at rest is about 160 c.c per systolic second in hyperthyroid patients the ventricle empties at a rate of 260 c.c per systolic second Catecholamine depletion by decreasing heart rate further increases the mean velocity of ejection to 290 c c. per systolic second (Fig 5) These rates of systolic emptying seen in hyperthyroid patients are comparable to those observed in normal man during strenuous exercise.

Myocardial energy requirements are determined by a complex interaction of forces. The cardiac work is decreased by virtue of the decreased afterload However this is more than compensated for by the fast heart rate the increased stroke volume the accelerated rate of isometric tension development and the increased rate of left ventricular ejection It would appear that these changes could account for most of the increased myocardial oxygen utilization observed in hyperthyroid patients.[23, 24] However recent studies suggest that myocardial energy metabolism may be altered in experimental thyrotoxicosis[43]

Hemodynamics in patients with heart failure

When heart failure supervenes during the course of thyrotoxicosis because of underlying heart disease or because of hyperthyroidism itself certain alterations in the hemodynamic patterns may be observed These are most apparent during exercise[43] The resting circulatory dynamics are not sufficiently different to be recognizably distinctive. The cardiac output is

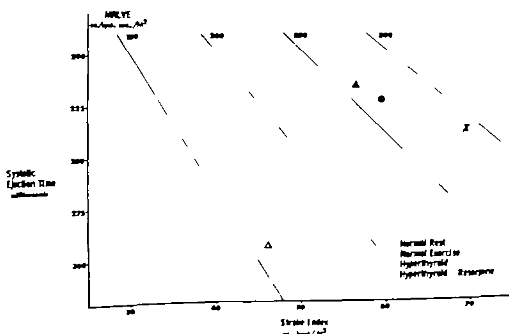


Fig 5 Mean rate of left ventricular ejection (*MRLVE*) in a group of hyperthyroid patients compared with that of a group of volunteers at rest and during exercise.

high and the heart rate is fast. The stroke volume may be normal or increased but more frequently it is low. From our very limited experience it would seem that the relationship between cardiac output and stroke volume which is seen in uncomplicated hyperthyroidism is maintained in some patients after heart failure occurs (Fig. 4).

During exercise the hemodynamics of heart failure become apparent. Hyperthyroid patients without cardiac decompensation have a proportionately normal increase in cardiac output and stroke volume during exercise. When patients with heart failure exercise, the cardiac output may increase slightly or not at all. The stroke volume usually remains unchanged and may actually decrease. In effect, heart failure in the hyperthyroid patient is reflected in the inability of the heart to meet the circulatory demands of stress. This does not mean that the resting cardiac output of hyperthyroid patients in heart failure is adequate, but rather that current methods of assessment have failed to reveal a distinctive abnormality.

Clinical picture

Much of the symptomatology and most of the clinical findings seen in hyperthyroid patients can be surmised from the physiologic alterations previously discussed. Thyrotoxic patients invariably have warm moist skin. This is obviously a direct result of the cutaneous vasodilatation and the greatly augmented skin blood flow. The superficial veins often appear engorged and this too must be due to the greatly increased volume of blood traversing the skin vessels as well as to the increased blood volume.[43] Tachycardia and a bounding pulse are seen in all thyrotoxic patients except in some who present with so-called masked hyperthyroidism. Many patients demonstrate a precordial heave and in some there is a discernible pulmonic shock. These are manifestations of the hyperdynamic circulation produced by cardioacceleration, increased stroke volume, and a fast ejection rate.

Almost invariably a venous hum can be heard at the base of the neck. Since cerebral blood flow is normal the hum must result from increased venous return from the extracerebral structures of the head and neck. This hum can often be heard with the patient in the supine as well as the sitting position, and on rare occasions may be heard over the chest in the second and third intercostal spaces.

A systolic ejection murmur is often audible at the base of the heart. This murmur frequently has a coarse, scratching quality and because of this rather distinctive feature, is often referred to by its eponym, the Lerman-Means murmur. When one considers that the rate of flow across the semilunar valves is increased 70 to 80 per cent above normal, the frequent appreciation of a systolic flow murmur is not surprising. Diastolic flow murmurs can also be heard on rare occasions (Fig. 6). These are probably of mitral origin since

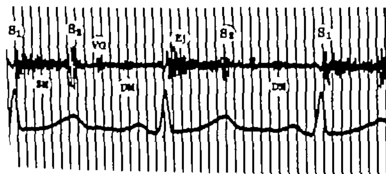


Fig. 6. Phonocardiogram from 40-year-old hyperthyroid patient demonstrating third heart sound (*VG*), systolic ejection murmur (*SM*), and diastolic flow murmur (*DM*). S_1 and S_2, First and second heart sounds. *EJ*, ejection sound.

they do not have the usual Carvallo's inspiratory accentuation Rapid filling or third heart sounds are frequently heard and usually an atrial gallop can be appreciated

Dyspnea is a common complaint of patients with Graves disease perhaps the most common While heart failure may be the cause of this distressing symptom in some patients it is probably more often due to weakness of the respiratory muscles and to altered lung mechanics.[44] Since there are many hemodynamic similarities between hyperthyroidism and exercise, it would be anticipated that the pulmonary capillaries would be suffused with blood as they are during exercise.[44] This would supply a ready explanation for the decreased lung compliance observed in thyrotoxic patients. In fact the pulmonary capillary blood volume is normal despite the greatly increased flow The mechanism responsible for this apparently important adaptive adjustment is not known

Electrocardiographic findings

Considering the magnitude of the circulatory changes induced by hyperthyroidism the electrocardiographic findings are surprisingly few Hyperthyroidism does rank as the third or fourth most common cause of atrial fibrillation and this is undoubtedly the most important electrocardiographic finding in thyrotoxicosis. It is most often seen in patients whose hearts are damaged by some other process but may also be seen in patients with uncomplicated hyperthyroidism The importance of hyperthyroidism in the genesis of atrial fibrillation is attested to by the fact that spontaneous reversion to normal sinus rhythm after adequate antithyroid treatment is the rule.[46, 47]

Voltage changes suggestive of left ventricular hypertrophy are sometimes recorded Postmortem studies would suggest that these changes are due to true myocardial hypertrophy however hormone induced changes in ventricular depolarization cannot be excluded

Generalized S-T segment and T wave alterations are commonly observed These changes consist of elevation of the S-T segment followed by terminal inversion of the T wave (Fig 7) A striking feature of these abnormalities is their evanescent nature. On occasion they can disappear and reappear over a period of several days.[48] The cause and significance of these changes has not been determined. P R prolongation is not unusual It is especially apparent when the P R interval is corrected for heart rate but gross delay in the atrioventricular conduction time is occasionally seen Notching and slurring of the P wave is frequent.

Hyperthyroidism as a cause of heart failure

It is obvious from the foregoing discussion that thyrotoxicosis severely stresses the myocardium When the burden of hyperthyroidism is superimposed upon a previously diseased heart congestive heart failure frequently results. Not only is the diseased heart subject to stress beyond its capacity but also the otherwise normal heart on occasion suffers the same fate Clinical studies have conclusively demonstrated that congestive heart failure sometimes does occur in young thyrotoxic patients who have no underlying heart disease[49] The mechanism by which hyperthyroidism produces heart failure in these patients has remained elusive.

Autopsy studies have shown ventricular hypertrophy as an isolated finding in 7 per cent of hyperthyroid patients.[50] Animal studies have revealed thyroid induced changes in the myocardium which range from areas of round cell infiltration to small areas of frank necrosis.[51] Whether these changes ever occur in the human thyrotoxic myocardium is not known

In considering the genesis of heart failure in hyperthyroidism biochemical studies are of particular interest. As previously mentioned myocardial oxygen utilization does not appear to be increased out of proportion to the increased load imposed by the high cardiac output. Although the rate of myocardial high energy phosphate production is not known it can be surmised from human skeletal muscle studies that ATP formation is not impaired[51] Myocardial utilization of high energy phosphate however appears to be markedly accelerated producing a grossly inefficient transfer of chemical energy to myocardial work[41] Under these circum

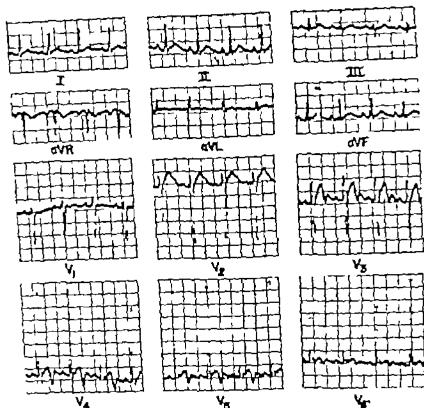


Fig. 7. Electrocardiogram from a 23-year-old hyperthyroid patient without evidence of organic heart disease.

stances depletion of high energy phosphate stores might be anticipated. Reduced concentrations of myocardial creatine phosphate and ATP have been reported by some investigators,[12] but not others.[13]

Both clinically and pathologically cardiomegaly has been observed in hyperthyroid patients. The existence of an increased stroke work in many patients with severe thyrotoxicosis undoubtedly plays an important role in the development of cardiac enlargement. Cardiomegaly induced by the greatly increased volume overload together with the defective utilization of energy sources are possible causes of heart failure in Graves' disease.

As previously implied, it is doubtful that altered renal function plays an important role in the production of congestive heart failure. In uncomplicated hyperthyroidism renal blood flow and glomerular filtration rate are equal to or slightly greater than normal. While it is possible that these rates of renal blood flow and glomerular filtration are inadequate in a clinical setting where the metabolic demands are greatly increased, this seems unlikely since the renal response to acute sodium loading is entirely normal.[15]

Summary

Hyperthyroidism is the most common cause of hyperkinetic circulatory disease. Thyroid hormone probably produces this high output state by inducing vasodilatation of the circulatory beds supplying muscle and skin. This hormone induced effect lowers the total peripheral resistance which increases cardiac output. The heart responds to the low peripheral resistance by accelerating the heart rate and augmenting stroke volume. In addition the thyroid hormone enhances ventricular contractility. These cardiac responses are generated by a direct effect of thyroid hormone on the cardiovascular system and are essentially independent of autonomic influence.

Thyrotoxicosis can induce congestive heart failure without complicating in

fluences Present information does not allow a full explanation of this phenomenon but improper utilization of energy by an oversized heart may be a contributing factor

Adequate treatment of this high cardiac output state whether or not it is accompanied by congestive heart failure cannot be properly accomplished without vigorous treatment of the underlying endocrine disorder Most adjunctive therapeutic measures presently recommended are of only slight and temporary benefit. Digitalis and diuretics can help control the manifestations of heart failure and should be used when these symptoms are present. Bed rest in a quiet environment is certainly more important in reducing the circulatory load of an already overstressed heart Reserpine and other autonomic blocking drugs cannot be recommended on a rational scientific basis There is little evidence that these agents have any salutory effect on the circulatory disease of hyperthyroidism

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Microvascular technique in coronary artery surgery

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Detailed studies of the pathologic anatomy of coronary artery occlusions were made soon after the nature of angina pectoris coronary thrombosis and myocardial infarction was generally recognized During the past three decades these studies have exhaustively established that total coronary occlusions are usually close to the ostia of the main arteries and are of short extent but that the stenosing arteriosclerotic process extends diffusely and in skip fashion down the coronary arteries It was a narrow focus on the total occlusion and disregard of the distal stenosing process that led to the early application and discouraging results of coronary endarterectomy Successful endarterectomies are usually those that terminate at normal distal intima The expected site of normal distal intima in the coronary arteries was not and is perhaps still not generally appreciated

During the past five years it has been this author s practice to dissect the arteries of fresh postmortem arteriosclerotic hearts specifically to examine the normal distal intima. Initial findings showed vessel size to be a most useful guide for predicting where the arteriosclerotic process would stop In a prospective study of 50 hearts abnormal intima was seen only once in vessels measuring 1 5 mm in diameter or less Endarterectomy cannot be successful in such small vessels The endarterectomy is an intraluminal arterial wound Uncovered collagen is its base An extensive endarterectomy heals as does any extensive wound by cicatrix Cicatrix of a thickness that would be physiologically meaningless in the aorta iliac femoral and even carotid arteries will occlude 1 5 mm arteries. Attempts to avoid formal endarterectomy or augment it with roof patching have not yielded acceptable patency rates even in patients selected by coronary arteriography of the highest quality

Clinical application of coronary bypass grafting the alternative to endarterectomy was not reported in this country until 1968 despite the fact that the principles and superior results of autogenous bypass grafts were well established in peripheral vascular surgery The problem was not one of principle but of technique cardiac as well as vascular Accurate arteriotomy cannot be performed on a moving vessel Although the right coronary artery has few branches and can safely be separated far enough off the surface to be kept immobile the distal segments which are suitable to receive a bypass graft are usually on the posterior surface of the heart and cannot be exposed without displacing the heart to such a degree that artificial support of the circulation is necessary Surgery on the distal segments of the left anterior descending artery always requires cardiopulmonary bypass because the anterior descending artery is bound to the interventricular septum by a continuous leash of branches and cannot be immobilized

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independently of the heart. Control of cardiac action became feasible when techniques of cardiopulmonary bypass were perfected. With extracorporeal circulation a still field can be obtained either by induced electrical fibrillation or by anoxic arrest. This author believes induced fibrillation is preferable and has used it exclusively in a series of 32 cases. In none of these cases has ventricular irritability or low cardiac output been a problem in the postoperative period.

As to vascular surgical technique, the reason that experimental reports of bypass grafting in dogs antedated clinical application by ten years is that microvascular technique was not employed. As has been stated, the 1.5 mm. arterial segments are generally those that are suitable for anastomosis, but it is not possible to perform an adequate arteriotomy or anastomosis on a 1.5 mm. vessel without magnification and special instruments. This author has found it best to use the operating microscope at a magnification of 16 times, and to use 9-0 nylon monofilament suture. Using this technique, this author has operated on 32 patients, 26 being NYHA class IV. D Angiography was not used to select distal circulation but only to establish the severity of occlusive disease. In 31 of these 32 patients, a normal distal segment measuring 1.5 mm. in diameter was found and end-to-side anastomosis performed. The site for anastomosis was determined by isolating a short segment of the left anterior descending artery 2 inches from the apex of the heart where the artery predictably would be normal. Once this normal segment was isolated the epicardium overlying the vessel was incised cephalad and the artery mobilized and examined externally until induration of the vessel was encountered. A 1 cm. area of the normal vessel was then isolated between temporary ligatures and arteriotomy performed. Usually the end of the internal mammary artery was utilized for anastomosis to the side of the anterior descending artery. The initial reason for selecting the internal mammary artery was that it is a good match in size to the distal anterior descending. The results of the anastomosis encouraged its continued use. It was striking that although the first nine patients operated on had right as well as left-sided disease, the single mammary anastomosis eliminated the anginal syndrome. By elimination of anginal syndrome is meant absence of angina despite cessation of vasodilator and beta blocking medication and in the face of great increase in activity. In the operating room an electromagnetic flow probe was used to measure flow through the mammary artery just prior to closure of the sternotomy. Flow through the artery averaged 50 ml. per minute. The postoperative courses of these patients were in striking contrast to those of comparably ill implant patients. Ventricular irritability was not a problem and ambulation within 48 hours proved to be feasible.

Re-establishing inflow to the anterior descending coronary artery by this technique was so easily managed that it was decided to simultaneously re-establish inflow to the distal right coronary artery in those patients having right as well as left-sided obstruction. The mammary artery was not chosen for the right-sided anastomosis because the distal right coronary artery is usually larger than the mammary artery. Furthermore because of the paucity of branches of the right coronary artery a long arteriotomy which facilitates anastomosis is especially applicable. Therefore a segment of saphenous vein was chosen as the graft and interposed between the side of the ascending aorta and the distal right coronary artery. Use of the saphenous vein segment allowed preparation of the graft by an assistant while the surgeon began the intrathoracic procedure. In the right-sided as well as in the left-sided anastomoses the principle of performing anastomosis to nonindurated segments of artery is most important. Postoperative angiography has confirmed that there will be retrograde flow through the stenotic proximal portion of the vessel right up to the site of proximal occlusion. This is achieved while not jeopardizing the graft and distal flow by anastomosing to a diseased vessel segment. In the 16 such operations performed to date, no patient was rejected because of angiographic findings. Surgically it was necessary to isolate the distal right coronary and its posterior descending and left atrioventricular branches in order to

find a suitable segment for arteriotomy and anastomosis However because of the larger size of these vessels as compared to the distal left anterior descending coronary artery and because of the longer arteriotomy use of the microscope was required in only 4 of these 16 cases.

The occasional necessity of instituting cardiopulmonary bypass urgently to assist the circulation soon after sternotomy led to the evaluation of the use of a saphenous vein segment for the anterior descending anastomosis The selection of the site for and the techniques of anastomosis were identical to that used for the internal mammary artery anastomosis however the results have not been as good Two of 5 patients having such anastomosis have had recurrence of angina the first recurring three weeks postoperatively and the second three months postoperatively In both cases angiography revealed that the grafts to the anterior descending had occluded It is of only small consolation that the recipient coronary vessels were not worse than their preoperative states.

In summary during the past 18 months 31 patients 26 being New York Heart Association Class IV and five being Class III have had bypass grafting by microvascular techniques to their anterior descending arteries. There have been three cases in which angina recurred following operation Two of these recurrences were in the group of five patients in whom a saphenous vein segment was used and one in the group of 26 patients in whom the internal mammary artery was used for anastomosis.

There have been five hospital deaths At least one of these is believed to be unrelated to the operation Her case history is cited as being representative of the type of patient in this series.

A 49 year-old diabetic Class IV D woman sustained her third myocardial infarction in May 1969 and was thereafter bedridden by congestive heart failure as well as her pre-existing anginal syndrome Coronary angiography in April 1969 had shown occlusion of the right and proximal left anterior descending coronary arteries with poor contractility of the left ventricle. On July 7 1969 the end of the left internal mammary artery was sutured to th sidee of the distal left anterior descending coronary artery and a segment of saphenous vein was interposed between the ascending aorta and distal right coronary artery The initial postoperative period was complicated by pneumonia which resolved rapidly She was fully ambulatory without symptoms of angina or congestive heart failure and ready for discharge on July 21 1969 when excruciating abdominal pain occurred Operation on July 22 1969 revealed thrombosis of the superior mesenteric artery with necrosis of the cecum and impending necrosis of the small intestine Right hemicolectomy was performed and the circulation to the distal superior mesenteric artery re-established by a saphenous vein segment interposed between the descending aorta and distal superior mesenteric artery Reoperation on July 23 confirmed the patency of the graft but revealed patches of necrosis diffusely along the bowel On July 24 the patient died

The other four deaths occurred 6 weeks, 3 weeks 10 days and 6 days after operation two of these being due to pulmonary and two to cardiac complications.

While projection of operative risk is difficult on the basis of the small initial series of patients, risk is probably in the range of 15 per cent.

The immediate benefits of this type of surgery are striking and have been sustained during the 18 month period Angina is usually eliminated activity increased and vasodilator and beta blocking medication discontinued

Early (2 to 3 months postoperatively) angiographic studies in 7 patients confirmed the patency of the mammary anastomoses to the left anterior descending coronary artery and in four patients of the vein anastomoses to the right coronary artery Two of five vein anastomoses to the left anterior descending coronary artery have been demonstrated to be occluded

Using microvascular techniques it appears that the coronary circulation of most patients gravely incapacitated by coronary arteriosclerosis can be augmented sufficiently to eliminate anginal symptoms and permit increase of activity

Effects on longevity will require protracted study

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A modified catheter tip for selective left coronary arteriography

The technique of selective coronary artery catheterization in h man patients was first described by Sones and Shirey Since their publication the procedure has become widely accepted and applied n many cardiovascular laboratories. The Sones technique has been n use n this laboratory for the pa t 2½ years and a fair degree of familiarity with t has been obtained

It has been noted that the catheter must be entered securely into the orifice of the left coronary artery (LCA) prior to injection of contrast agent in order to obtain clear opacification of this vessel This is generally accomplished by bending the catheter on the aortic v lve cusps so that the tip curves back toward the LCA. The tip itself must then be caught n the orifice and advanced firmly into the lumen of the LCA. Frequently this has been difficult to accomplish To overcome this, a new catheter tip was devised A shown n Fig 1 (top) a tip-forming wire is bent to form two angles each approximately 60 degrees. No 7 5 French Sones Positrol catheters (U S Catheter and Instrument Co. Glen Falls N Y) are autoclaved with the wire in place, as shown Fig 1 (bottom) The wire rema s n place until the time of catheter insertion When the catheter is advanced nt the ascend ng aorta, the tip reassumes the configuration imparted by the wire The catheter is bent on the aortic valve at the proximal angle and the tip then points toward the LCA orif ce. It is usually possible to manipulate the catheter well into the LCA without further difficulty (Fig 2)

To date this type of catheter has been used in 50 patients. In all instances, the left coronary artery has been entered and excellent opacification of the left coronary artery has been obtained. No tendency

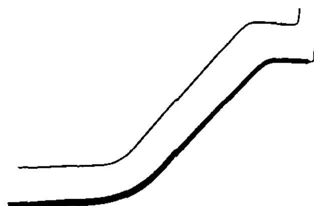


Fig 1 Top Tip-forming wire Bottom, No. 7.5 Sones Positrol catheter with tip-forming wire n place.



Fig 2 Left anterior oblique view of Sones catheter securely positioned in the left coronary artery

of the catheter to recoil from the orifice during injection has been observed once the catheter has been securely engaged. It has been the impression that the amount of time spent in manipulation while trying to catheterize the LCA has been *significantly* diminished by the use of this type catheter.

In a few instances, difficulty was encountered in entering the right coronary artery orifice. This occurred primarily when the origin of the vessel was quite low, necessitating a sharp curvature of the catheter just above the aortic valve. In those cases, the catheter was replaced with a conventionally shaped Sones catheter and the studies were then completed.

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Hemolysis after heterograft and prosthetic valve replacement

Intravascular hemolysis is a recognized complication of heart valve replacement and various prosthetic devices have been implicated in its production.

The early report by Stohlman and colleagues[1] of hemolysis occurring in dogs which had received Lucite ball valves was subsequently followed by descriptions of traumatic red cell damage due to artificial valve leaflets, caged ball valves,[2-10] and disc valves. The hemolytic process was often of sufficient severity to produce a significant anemia. Considerable urinary iron losses in the form of hemoglobin, hemosiderin, and ferritin as a consequence of intravascular hemolysis contributed to the production of the *anemia.*[10,16] In *some cases* it was possible to elevate hemoglobin levels by iron therapy thus obviating the need for further surgery.[11]

More recently, studies on patients with valvular heart disease, particularly aortic stenosis and incompetence, have also revealed the presence of intravascular hemolysis.[16-18] No close correlation has been established between the severity of hemolysis and such factors as the presence of valve calcification or the type and severity of the lesion. Renal hemosiderosis and increased urinary iron losses have been demonstrated in some of these patients, proceeding to iron deficiency in isolated cases.[16]

A study of *iron metabolism and red cell survival* was recently undertaken in this center[20] comprising three groups of patients: (1) 22 preoperative patients with valvular heart disease, (2) 30 patients who had received heterograft valves, and (3) 8 patients with Starr-Edwards prostheses.

Group 1. Sixteen of the 22 preoperative patients showed hemolysis (^{51}Cr half-life [t½], *17 to 24* days) but none was anemic. Hemodynamic studies were performed on all patients prior to operation, and valve calcification was graded 0 to 3+ at operation. Again no significant correlation could be established between the degree of hemolysis and these assessments. Nineteen patients had increased urinary iron excretion (mean 0.51 mg. per day; *range 0.15 to 2.12 mg. per day; normal values in this* center 0.05 ± S.D. 0.03 mg. per day), but the degree of urinary iron loss did not correlate significantly with the degree of hemolysis.

Group 2. The 30 patients with heterograft valves were investigated 3 to 9 months postoperatively. All patients received aortic heterografts: 28 for aortic valve disease, one for mitral valve disease, and one had a double replacement for mitral and aortic valve disease. Twenty-three patients showed normal valve function on clinical examination and 22 of these had normal red cell survival. Seven patients showed residual aortic incompetence of varying degree (see Table I).

Thus 25 of the 30 patients had no hemolysis and in the other 5 patients subclinical hemolysis only

Table I. Red cell survival and heterografts

Case	*Hemolysis (^{51}Cr t½, normal 25 to 32 days)*	*Valve incompetence*	*Comment*
1 to 3	17, 22, 22.5	Moderately severe	—
4	20.5	Minimal	Dacron ascending aorta
5	23	0	Pacing catheter
6 to 8	25, 25, 27	Minimal	—
9 to 30	25 to 32	0	—

Table II Patients with Starr Edwards prostheses

No. of cases	Hemolysis (^{51}Cr t½ in days)	Valve incompetence
2	10 10 5	Moderately severe
2	14 16	Mild
2	17 24	Minimal
2	25 10	0

was detected and appeared to be related to valve incompetence or the presence of other foreign material in the circulation

Urinary iron losses decreased exponentially with time, reaching normal levels within 10 months.

Group 3 Our experience with Starr Edwards valves is similar to that of previous workers. All 8 patients presented with symptoms referable to the cardiovascular system or to anticoagulant therapy and hence represent a more selected group In consequence the results are somewhat worse than those of previous reports. Seven of the patients were hemolyzing and 6 of these showed valve incompetence (see Table II). In 2 patients anemia wa severe enough to be a major indication for removal of the Starr Edwards prosthesis and replacement with a heterograft.

A comparison of Tables I and II shows that prosthetic valves appear to produce more severe hemolysis than heterografts with a similar degree of clinical incompetence In addition one patient with a Starr Edwards valve and no clinical evidence of valve incompetence showed very marked hemolysis. This phenomenon, though described previously for prosthetic valves, [4] has not been observed in any of the patients with heterografts. Urinary iron losses n this group reflected the degree of hemolysis (mean 4 15 mg per day range 0.2 to 10 6 mg per day).

These findings support the belief that red cell fragmentation is largely the result of turbulent blood flow caused by deformed or rigid val e leaflet Valvular incompetence and contact of red cells w th the synthetic materials used in val e prostheses appear to be further factors in red cell trauma. Thu a severe degree of hemolysis seems to occur in situa tions where a turbulent jet of blood mpinges on material such as Teflon or Dacron.[11] Nevaril and colleagues[12] applied laminar shearing forces to red cells in vitro and produced a hematologic picture similar to that in patients with leaking val e prostheses.

The evidence therefore implicates a number of causative factors in the hemolytic process, the importance of each one varying in different patients. Heterografts produce little turbulence[13] and the above evidence suggests that they do not beha e like "foreign material" in the circulation. It is therefore concluded that in regard to hemolysis they resemble human valves, both when hemodynamically normal and when malfunctioning

In 10 of the 30 patients with heterograft val es the investigations have been repeated at times now ranging from 9 to 17 months after operation. No patient has developed hemolysis in the interim and one of the five patients above has ceased to hemolyze (Case 4 Table I). It is felt that, in this patient re-endothelization of his Dacron graft has occurred, thus reducing mechanical trauma to red cells Urinary iron loss in all 10 patients has returned to normal levels. A detailed report of the iron metabolism in the three groups of patients discussed is in preparation.

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Heart tone

There is alw y considerable discussion concerning the definition of cardiac tone. These definitions include entirely physical (nonlife-dependent) and/or biologic (life-dependent) phenomena. The definition of any ord is valuable only for communication, so that in discourse all will hav a clear understanding of the meaning of the word—a mere symbol in writing and speech. Nevertheless, clear understanding of its meaning is necessary for satisfactory communication.

Because of confusion concerning the meaning of the ord "tone and in order that those who read this annotation ca understand the concept discussed, w shall define cardiac "tone as used herein Those ho dislike the ord are privileged to substitute another ord for t and/or redefine it However the concept as described defines our thoughts or ideas. W introduce the term cardiac tone to mean the tightness due to active, biologic, "living physicochemical phenomena with which the cardiac muscle squeezes or tightens on he blood within its respective chambers t the end of diastole. Thus, cardiac tone is defined as the active tension of the cardiac myocytes due to living metabolic phenomena, and not as passive nert physical resistance to expansion of the chambers, stretch of the tissues of the heart, or "elastic recoil of its molecules. There is no doubt that inert, passive physical factors consort ith activ "tightening or tension of the muscle which is dependent on activ organized metabolic life processes. Although we shall confine our discussion to the cardiac tone t the end of diastole, the time course of cardiac tone during the cardiac cycle is extremely important and needs meticulous integration with ll points on the pressure-volume time diagrams[1] of the cardiac chambers.

From these concepts of tone of the myocardium, the level of pressure in any one chamber t the end of diastole reflects the tension of the myocardium or the myocytes of the heart t that time. It, therefore, behooves the one measuring and interpreting the end-diastolic pressure to determine hat part of this pressure is dependent pon activ tightening or tension of the myocardium and what part is passive. Such concepts have been discussed elsewhere for ones.

Although ttempts ha been made to dispel the belief *it is often* and erroneously accepted that an elevated end-diastolic pressure invariably indicates myocardial failure. Although an elevated end-diastolic pressure may indicate failure of ventricle, it can also indicate an increase in myocardial tone, e., an increase in activ tension or squeeze of the myocardium upon the blood within the chambers t the end of diastole.

Thus, high activ myocardial tension is not necessarily sign of congestiv heart failure but could be due to a high level of myocardial tone Activ metabolically determined tension can be high at the end of diastole in states with either relatively large or relatively small levels of olume of the cardiac chamber The tone of the myocardium can

Table I Effect of selected drugs and paired pacing on the cardiac tone

Stimulus	LVEDP	LVEDV	Contractility	Cardiac tone	Reference
Angiotensin II	↑	↑	↑	?	4 5
Norepinephrine	↑	↓	↑	↑	6
Propranolol	↑	↑	↓	?	7
Isoproterenol	↓	↑	↑	↓	4
PGE	↓	?	↓	?	8
E. coli endotoxin	↓	?	↓	?	9
Paired pulse	↓	→ or ↑	↑	↓	10

be high or low with the heart small or dilated depending upon the setting or state of the actomyosin fibers and their connecting bridges. Because of insufficient knowledge of the physicochemical phenomena of the function of the myocardium the mode of operation of the myocardial acti and myosin fibers and interconnecting bridges mu t be left to one s imagination

For any given ventricular volume the nonbiologic tension is not likely to change. This may explain the differences seen in pressure-volume-time relationships between live and dead hearts. It is the active tension which is fundamentally responsible for the myocardial pressure-volume-time relationships in the intact living heart. Thus, if the ventricular volume remains constant, changes in pressure will reflect changes in active tension. For example if the heart dilates and left ventricular end-diastolic pressure (LVEDP) decreases th n active tension is reduced whereas the tone is increased when there is a reduction in ventricular volume and an increase in pressure. If the heart dilates or decreases in size and the end-diastolic pressure remain the same then the cardiac tone remains unchanged unless there is a reciprocal relationship between active and passive variation in the state of the wall of the cardiac chamber Obviously when the heart dilates and end-diastolic pressure rises passivel only then cardiac tone is reduced.

However if the ventricular volume and left ventricular end-diastolic pressure either increase or decrease together one cannot be sure how much of the pressure change is active unless the pressure-volume-time relationship of the heart can be determined in the non iable t te for precisely the same conditions. Table I summarizes examples of changes in cardiac tone secondary t pharmacologic (norepinephrine, isoproterenol) nd pa red pulse stimulation. Four examples are also noted which changes in cardiac tone n response to agent remain unknown. Furthermore t can be seen from Table I that tone, contractil ty and volume can be independent variables.

It must be remembered that the increased left ventricular end-diastolic pres ure found n left ventricular congestive heart failure is always associated with an increase in left ventricular end diastolic volume (LVEDV) Therefore one does not know whether the increase in left ventricular end-diastolic pressure is due to a relatively high myocardial tone or whether the end-diastolic pressure is passively increased due to high left atrial and systemic venous tone and pressure while the coexisting ventricular myocardial tone is low

Therefore, in hemodynamic interpretation of myocardial function in experiments and in disease, one must consider myocardial or heart tone as defined above Thus, a high left ventricular end-diastolic pressure does not *a priori* indicate the presence of left ventricular congestive heart failure.

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Countercurrent exchange in the small intestine

The existence of countercurrent exchange of materials between arterial nd enous segments of capillaries is firmly established in the mammalian kidney and the swimbladder of many fishes A countercurrent mechanism is dependent pon the close anatomical association of the arterial and enous limbs of ascular loop. I the tw aforementioned organs the exchange takes place in the so-called *rete mirabile* bere arterial" and oous segments of capillaries closely intermingle.

The ascular arrangement of the intestinal mucosa, particularly of the illi, suggests the possible existence of countercurrent exchange of easily diffusible material in that part of the intestine. Thus, the arterial supply to each villus usually consists of single tortuous essel running in the central part of the illus ithout branching (see Fig 1). Close to the tip of the illus the ascending essel arborizes into dense subepithelial network of capillaries. The capillaries collect into enms t the base of the illus

It is clear that the main direction of blood flow in the subepithelial capillary network must be opposit to that of the central arterial vessel. The distance between the arterial and enous parts of this ascular loop is estimated to be 10 to 20 µM Such distance can be tra ersed by easily diffusible agents in fraction of second

A series of experiments as therefore performed on cats in order to test the proposed countercurrent hypothesis The four main experimental evidences for this mechanism ill be summarized below (point 1 to 4) For more detailed description and discussion of these and some additional points, the reader is referred to the papers by Lundgren, Kampp and Lundgren, Kampp, Lundgren, and Nilsson, and Kampp, Lundgren, and Sjostrand [?]

1 I an attempt to nalyze blood flow distribution in the small intestine of the cat by means of the inert gas washout technique it as demonstr ted that the composite y curve registered after intra-arterial injection of Kr solution, exhibited large and extremely fast first component I terms of blood flow such component ould indicate that 30 to 50 per cent of resting" total intestinal blood flow is diverted to either arteriovenous blood flow shunts or to an intestinal region where flow amounted to 400 to 800 ml. per minute × 100 Gm. An alternati explanation for this obs tion is that the fast component reflects the extra ascular short-circuiting of the injected gas mucosal countercurrent exchanger

Similar gas shunts ha been demonstr ed in the kidney probably reflecting countercurrent exchange between the t limbs of the asa recta loops

2. It w argued that if krypton as short-circuited extra ascularly between the t limbs of the mucosal ascular loops, other easily diffusible substances should beha e in similar manner I order t obtain evidence for such a shunting of oxygen, the enous appearance time of intra-arterially injected oxygen was compared w th that of methemoglobinemic red cell administered in an identical

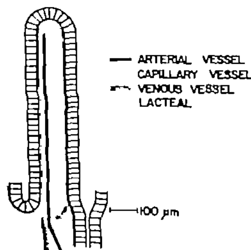


Fig 1 Schematic dra ing of the ascular anatomy of cat illus. The capillary essels of the figure denote dense capillary network lying just beneath the intestinal epithelium. Note that the ascending arterial vessel and the descending capillary network and enous essel form hairpi vascular loop (From Lundgren.)

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through 4 summarize the main part of the experimental evidence for the existence of a countercurrent exchange in the intestinal mucosa of the cat. Although alternative explanations can be suggested for each of the different observations, a countercurrent exchange seems to be the only mechanism which adequately explains all these findings.

The functional significance of the countercurrent mechanism is not yet clarified. It seems a priori likely, however, that the presence of a countercurrent exchanger in the intestinal mucosa must affect intestinal absorption. The transport of a substance, active or passive, from the lumen across the intestinal epithelium into the subepithelial capillary network of the villus, will increase the concentration of the solute in the venous blood draining the villus and consequently create an arteriovenous concentration difference. Because of the vascular anatomy of the villus, a fraction of the substance can then be expected to diffuse extravascularly to reach the central ascending arterial vessel, as schematically illustrated in A of Fig. 2. Thus, the solute is again brought toward the tip of the villus. The effectiveness of the countercurrent exchanger to delay net absorption of substances in such a way must depend on factors such as the distance between the two limbs of the hairpin loop, the permeability of their walls, the linear velocity of blood in the vessel, the diffusion characteristics of the solute, etc.

Evidence for a delayed absorption of the inert, lipid-soluble substances antipyrine and krypton during low and moderate blood flow levels within the intestinal tissues was presented in the present study (see point 4). These findings are corroborated by the observation in earlier studies that gaseous hydrogen, when introduced into the lumen of the small intestine, is absorbed extremely slowly if at all.[10]

Furthermore, a study of Grim and associates[5] may indicate that water is short-circuited in the intestinal countercurrent exchanger. In this study the intestinal lumen was lavaged for 0.5 to 120 min. by a fluid containing an approximately constant concentration of D_2O. It was found that the concentration of D_2O in the mucosa and in the venous effluent from the intestinal segment was surprisingly low, amounting at most to 25 and 5 per cent of that of the intestinal lumen, respectively. The authors discuss at length possible explanations for these observations and conclude that they may be explained by either a low mucosal capillary permeability to water or an extensive arteriovenous shunt carrying at least 35 per cent of the total blood flow through the intestine. In the light of the present investigation it seems likely that the aforementioned observations of the concentration of D_2O in the intestinal mucosa and the mesenteric venous blood are caused by the presence of a mucosal countercurrent exchanger. This opinion is corroborated by the finding that no significant shunting of blood seems to occur in the dog intestine.

The existence of an intestinal countercurrent exchanger may affect not only intestinal absorption of materials but also, in certain situations, substances that reach the exchanger via the arterial blood. In the presence of a higher arterial than venous concentration of a solute, the substance may be short-circuited extravascularly and more or less excluded from the villus, as shown in B of Fig. 2. Such a concentration difference between artery and vein may be induced in two ways, i.e., by increasing the arterial concentration or by decreasing the venous concentration of the solute. In the present series of experiments, the arterial concentration was increased by intravascular administration of various solutes.

It is probable that an arteriovenous concentration difference of blood-borne solutes is often established in the intestine of the intact organism by diffusion from the subepithelial capillary network into the intestinal lumen, thus tending to reduce their concentration in the venous effluent. The countercurrent exchange diffusion between the arterial and venous vessel of the villi prevents to some extent such a loss of solutes, from the blood into the lumen of the gut, and establishes a continuous concentration decrease of the substance from the bases towards the tips of the villi. The mechanism is selective in the sense that those substances that would most easily traverse the intestinal epithelium (lipid-soluble material of small molecular weight) will also be most efficiently "shunted" in the mucosal countercurrent exchanger.

The mechanism illustrated in Fig. 2, B will presumably hinder the net blood transport also of oxygen to the tips of the villi, at least at low and moderate flow levels, and create a decreasing oxygen pressure within the villi from their bases towards their tips. This assumption is corroborated by the experimental findings that strongly suggest the existence of an extravascular shunting of oxygen in the small intestine (see point 2). The proposed oxygen gradient in the villi may be a factor of importance in explaining the well-known rapid turnover of intestinal epithelial cells.

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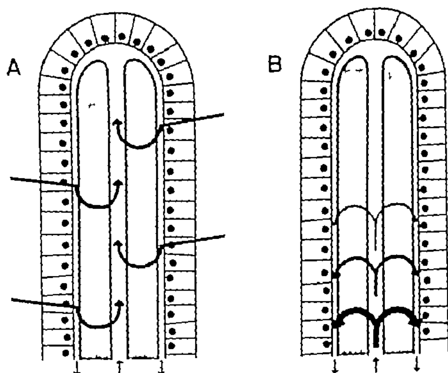


Fig. 2. The functional implications of the mucosal countercurrent exchanger schematically illustrated. The intervascular distance is greatly exaggerated for the sake of clarity. For details, see text. (From Lundgren.[27])

manner. Although red cells have been shown to pass more rapidly through the splanchnic vasculature than plasma, it was found that oxygen appeared 1 to 2 sec. earlier than the labelled red cells in the mesenteric vein during "resting" conditions. This observation is explained by the countercurrent hypothesis in the following way. Oxygen is "shunted" in the mucosal countercurrent exchanger and can therefore appear earlier in the mesenteric vein than the labelled red cells which remain within the vessel and consequently have to pass through the mucosal vascular loops.

Results similar to those obtained in the present study on the intestine have been reported for the kidney.[14,34] The early appearance of oxygen in the renal vein has been taken to indicate a countercurrent exchange diffusion of oxygen between the limbs of the vasa recta loops.

3. A countercurrent exchanger acts as a "hindrance" for the net transport of an easily diffusible substance along the long axis of the vessel whenever a concentration difference of the substance exists between the two limbs of the hairpin vascular loop (see *B* of Fig. 2). If a mucosal countercurrent exchanger exists and if a gradient of an easily diffusible substance is created by intravascular administration of the substance, one would expect to find a comparatively lower concentration of the solute in the tips of the villi than at their bases. The predicted pattern of distribution could be demonstrated for antipyrine-^{14}C and 4-iodoantipyrine representing lipid soluble substances.

A similar distribution pattern, although less pronounced, was seen after intravascular administration of urea-^{14}C and ^{86}Rb (lipid-insoluble, pore-restricted substances), suggesting that these two solutes are also "shunted" extravascularly in the mucosal countercurrent exchanger. The aforementioned quantitative difference between the lipid-soluble antipyrine-^{14}C and 4-iodoantipyrine and the lipid-insoluble urea-^{14}C and ^{86}Rb was expected on grounds of their different transcapillary diffusion characteristics.

Intravascularly administered krypton and rubidium have been shown to be excluded from the renal papilla,[14] in all probability due to the countercurrent diffusion exchange of these substances, taking place between the limbs of the vasa recta loops.

4. A countercurrent exchanger will act not only as a "barrier" for the entry of diffusible material from the blood stream into the tissues around the tips of the vascular loops, but it can also be expected to act as a relative "hindrance" for the exit of such substances which have entered the tissue supplied by the hairpin loop (see *A* of Fig. 2). The existence of a countercurrent exchanger will therefore also *delay* the washout of diffusible solutes from the vascular loop.

Such a comparatively slow elimination from the villi was, in fact, demonstrated at low and moderate intestinal blood flow level for krypton, for antipyrine-^{14}C and for urea-^{14}C. Furthermore it was demonstrated in preliminary experiments that krypton, deposited as a thin film of fluid between the mucosal surface and a diffusion barrier (Mylar) was eliminated at a rate as low as when krypton had been deposited in a similar manner on the serosal surface,[7] despite the fact that the blood flow is considerably higher at the mucosal surface.

A delayed elimination from the renal papilla has been demonstrated for krypton[36] and for hydrogen.

The results presented above under points

ENZYMIC BIOCHEMISTRY OF THE ARTERIAL WALL AS RELATED TO ATHEROSCLEROSIS. By Tibor Zemplenyi, M.D., D.Sc., London, 1968, Lloyd-Luke (Medical Books) Ltd. 273 pages. Price 90 Sh.

The main purpose of this book is to present an account of the biochemistry of vascular enzymes in relationship to atherosclerosis and to the author's extensive work at the Institute for Cardiovascular Research in Prague. The material is presented in three parts: (1) general properties of the enzymes, (2) special problems of the enzymes studied by the author, (3) lipolytic activity of the vascular wall. Although this is a brief book, all of the known vascular enzymes are included, extensive documentation of comparative atherosclerosis is provided, and many of the factors changing enzyme activity are discussed. This monograph will be of most interest to students of atherosclerosis and enzymology.

ATLAS ANGIOGRAPHISCHER UND EXPERIMENTELLER DER RÖNTGEN AORTOARTERIOGRAPHIE. By L. Wierny. Berlin, 1969. Veb Verlag Volk und Gesundheit, 73 pages.

This small volume of 73 pages gives a quite comprehensive presentation of arteriography of the lower extremities from the abdominal aorta.

The author points out in his preface that in spite of the numerous recent publications on arteriography there was no adequate information available about the diagnostic advantages and limitations of the various methods as well as results in a numerically adequate sample. It is the main aim of this monograph to provide this information, with critical discussion of technical, anatomical, and functional problems. While the book is based mainly on the author's large material, it lists 177 references, starting with E. Haschek and O. Lindenthal, in 1896, the first work with the application of x-ray for demonstration of blood vessels.

The book contains the following chapters: "Method" (including thorough discussion of complications), "Results" (including sex and age distribution, localization and types of occlusions, segmental distribution, and renal artery involvement in disturbances of peripheral circulation). The next chapter, "Collateral Circulation," goes beyond the technique of arteriography although this is, of course, considered too. It discusses also the physiologically and clinically important problem of development and types of collateral circulation. The final chapter, "Significance of Arteriography for Vascular Surgery," describes the site, extent, and vascular condition above and below the site of obstruction is discussed in regard to the indications, choice, and therapeutic results of the various surgical procedures.

While the material is naturally a preselected sample, it is large enough for meaningful and quite detailed statistical analysis. The percentage distribution of obstructions in 900 extremities was: aorta, 3.7 per cent; iliac artery, 29.6 per cent; femoral artery, 63.7 per cent; lower leg arteries, 53.4 per cent; there is further breakdown into arteria poplitea, tibialis anterior and posterior and arteria peronea. The age distribution is given for every artery. The peak of all vascular lesions occurred in the sixth decade.

The numerous illustrations are of excellent quality.

DYNAMICS OF THROMBUS FORMATION AND DISSOLUTION. Edited by Shirley A. Johnson, Ph.D. and M. Mason Guest, Ph.D. Philadelphia, 1969. J. B. Lippincott Company. 376 pages. Price $15.50.

This monograph represents the proceedings of a conference held in Washington, D.C., on Aug. 31, 1968, on thrombus formation and dissolution. The many participants were from the United States and foreign nations. Among the 24 subjects discussed were historical review of the problem, fine structure of the capillaries, microscopic characteristics of thrombi and hemostatic plugs, thrombogenic elements in arterioles, the role of subendothelial components in thrombosis, properties of the platelet membrane, protein synthesis and platelet function, and micromolecular inhibitors of fibrinolysis. A short but useful bibliography is appended to each of the 24 papers. The book consists of a series of relatively short but very good papers. Unfortunately, no discussions by the attending group are included. These informal discussions are usually the most interesting aspects of symposia. This is a good book on an extremely important subject.

CEREBRAL VASCULAR DISEASES, Transactions of the Sixth Conference. James F. Toole, Chairman, Robert G. Siekert and Jack P. Whisnant, Editors. New York, 1968. Grune & Stratton, Inc., 280 pages. Price $8.75.

These proceedings summarize the Sixth Conference on Cerebral Vascular Diseases. The conference was held in Princeton, N. J., Jan. 10 through 12, 1968. It conforms to the format of the previous conferences, being concerned with current concepts, research, and clinical practice. The subjects discussed were identification of the stroke prone;

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Book reviews

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The numerous illustrations are of excellent quality.

DYNAMICS OF THROMBUS FORMATION AND DISSOLUTION. Edited by Shirley A. Johnson, Ph.D and M. Mason Guest, Ph.D Philadelphia, 1969 J. B. Lippincott Company 376 pages. Price $15.50.

This monograph represents the proceedings of a conference held in Washington, D.C., on Aug. 31, 1968 on thrombus formation and dissolution. The many participants were from the United States and foreign nations. Among the 24 subjects discussed were historical review of the problem, fine structure of the capillaries, microscopic characteristics of thrombi and hemostatic plugs, thrombogenic elements in arterioles, the role of subendothelial components in thrombosis, properties of the platelet membrane, protein synthesis and platelet function, and micromolecular inhibitors of fibrinolysis. A short but useful bibliography is appended to each of the 24 papers. The book consists of a series of relatively short but very good papers. Unfortunately no discussions by the attending group are included. These informal discussions are usually the most interesting aspects of symposia. This is a good book on an extremely important subject.

CEREBRAL VASCULAR DISEASES, Transactions of the Sixth Conference. James F. Toole, Chairman, Robert G. Siekert and Jack P. Whisnant, Editors, New York, 1968, Grune & Stratton, Inc. 280 pages. Price $8.75.

These proceedings summarize the Sixth Conferences on Cerebral Vascular Diseases. The conference was held in Princeton, N. J., Jan. 10 through 12, 1968. It conforms to the format of the previous conferences, being concerned with current concepts, research, and clinical practice. The subjects discussed were identification of the stroke prone

fluid dynamics in macro- and microcirculation respiratory control and cerebral circulation; primary intracerebral hemorrhage aids for the diagnosis of cerebral vascular diseases dementia and cerebral vascular disease surgery in occlusive cerebral vascular disease and a progress report of the joint study of extracranial arterial occlusion. The progress report is particularly interesting in that the data on patients receiving medical or surgical care are summarized The reader can establish his own opinion of the relative merits of both approaches to management. The data and discussions also reveal the gaps in the study Unfortunately the accuracy and reliability of the data upon which the analysis was based are not clear The reader must erroneously assume that all data introduced into the statistical analyses are accurate. Furthermore, the number of patients studied is still small This publication is valuable and of considerable interest to all physicians who are concerned with cerebrovascular problems.

Prosthetic Heart Valves. Lyman A. Brewer III M D Editor-in-Chief Springfield, Ill 1969 Charles C Thomas, Publisher 909 pages. Price $12.50.

These are the proceedings of the Second National Conference on Prosthetic Heart Valves sponsored by the Society of Thoracic Surgeons and the National Institutes of Health and held in Duarte, Calif Sixty three papers were presented with almost 400 participants in attendance. The book is divided into five sections (1) valve structure and testing (2) materials and myocardial function (3) clinical experience (4) results and complications and (5) valve grafts and general discussions. The number of separate papers included in each section is about equal. The participants were leaders in cardiac surgery from the United States with a few from foreign countries. The subjects covered in this 900 page book include the most important aspects of this problem in surgery The presentations are good with each paper being well illustrated and supported by a short but pertinent bibliography Unfortunately very little discussion by the audience is included In fact, each paper is usually only appended by a brief remark by the chairman of the section. As would be expected, the subjects discussed are already well known to those who follow the medical literature closely Nevertheless, it is convenient and extremely useful to have all of this material available in a single volume. This is a very good book which should be not only useful to cardiac surgeons but all cardiologists. It is a good reference book on the subject for all physicians and medical students interested in prosthetic heart valves and their applications.

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Editorial

Ischemic cardiomyopathy

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In defining the cardiomyopathies, disease of heart muscle due to ischemia is usually not included. Indeed, the term cardiomyopathy is not used when coronary arterial disease and myocardial ischemia are present.[1-4] However, the degenerative changes of the myocardium due to inadequate blood supply comprise a true myopathy. They often result in a dilated heart with a protodiastolic gallop rhythm, tachycardia, and the symptoms and signs of intractable congestive heart failure among the other clinical manifestations of the cardiomyopathies. The large dilated heart can be demonstrated roentgenographically, and the electrocardiogram can reveal many abnormalities due to myocardial degenerative phenomena. The prognosis is grave and the poor response to therapy and other aspects of management is much the same as with the other cardiomyopathies. The entity, therefore, of ischemic cardiomyopathy should be accepted and recognized in view of the vast similarities to the other cardiomyopathies.

Ischemic cardiomyopathy is a common and interesting entity. Although typically a disease of older people with arteriosclerotic disease of the coronary arteries, it does occur in younger people. The etiology is primarily coronary artery disease with the associated impairment of blood flow to the myocardium. Other causes include difficulty in oxygen hemoglobin dissociation, metabolic diseases, hypertension, etc. The natural history of ischemic cardiomyopathy is fairly typical. The onset is usually associated with angina pectoris of increasing severity and gradual cardiac enlargement, with or without the development of one or more myocardial infarctions with scar formation. However, one may see a patient in the final stages of heart failure due to ischemic cardiomyopathy from whom no historical clue can be extracted as to the precise etiology of his disease. The rate of development and the extent of damage vary among patients. The clinical course may be modified by the elegance of management and the thoroughness with which the patient follows his therapeutic regimen.

The management of ischemic cardiomyopathy, in general, is that for any other type of cardiomyopathy but includes management of the coronary artery and other associated diseases and the associated impairment of myocardial blood flow. In

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addition attempts must be made to reduce the work load placed on the weak or failing pump due to the muscle disease. Cardiologists who have been in practice for many years have not only observed ischemic cardiomyopathy develop but have been impressed with the many exciting and challenging problems it offers. Early recognition of coronary artery disease is important so that vigorous and prompt introduction of all measures available can be instituted to improve the coronary circulation and prevent the development of muscle damage or ischemic cardiomyopathy. With full cooperation of the patient and his family much can be done for the prevention, delay of development and treatment of this disease entity.

With careful consideration of the cardiac disease due to coronary artery disease it becomes evident that ischemic cardiomyopathy is a true cardiomyopathy with a broad spectrum of pathophysiologic and clinical manifestations. The similarities to the other cardiomyopathies, such as idiopathic cardiomyopathy, are readily recognized. Thus myocardial ischemia, one of the most common disease states of man, should be included among other etiologic factors in the production of cardiomyopathies. Ischemic cardiomyopathy is the most common type of cardiomyopathy in Europe and the United States. Remember principles in diagnosis and treatment indicated in other types of cardiomyopathy should be seriously considered in the management of ischemic cardiomyopathy.

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Clinical communications

Vectorcardiographic study of the QRS loop in patients with left anterior focal block

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In recent years, there has been general agreement that the most common cause of left axis deviation (L.A.D.) is the left anterior focal block. This opinion is substantiated by several clinical and electrocardiographic-pathologic correlative studies[1-6] and by experimental work on canine and primate hearts.[7]

While electrocardiographic criteria for diagnosis of this conduction abnormality have been proposed, its vectorcardiographic aspects have so far received little attention. The present paper is concerned with the vectorcardiographic findings in 40 patients aged 45 or over whose electrocardiogram was suggestive of a left anterior focal block.

Methods

Spatial vectorcardiograms were recorded using the McFee Parungao axial system (Hewlett Packard Vectorcardiograph System 1520 A). The frontal horizontal and left sagittal loops as well as the scalar tracings X Y and Z were photographed by means of a Polaroid camera. The upper frequency response of the recorder was set at 200 c.p.s. and the loop was interrupted either every 2.5 msec. or 5 msec. The sensitivity was adjusted at 20 or 10 mm per millivolt and the 3 orthogonal scalar tracings were recorded at a speed of 100 mm per second. For better delineation of initial forces, a fivefold amplification of the isolated QRS loop was also recorded. Timing of the various points of the loop was obtained by counting dots on the photograph from the onset of QRS. Since inaccuracies of timing owing to haziness around the E point are inherent in this method of determining instantaneous vectors[8] the determinations were checked with the scalar tracings so that the three planar instantaneous vectors of the same timing coincided with one another in their coordinates.

The duration of the QRS loop was measured and the direction and magnitude of the following vectors were determined in each of the three projection planes the

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maximal QRS vector and the instantaneous vectors at 10 20 30 40 50 and 60 msec after the onset of QRS The measurements of vector angles in each plane were made with a frame of reference in which the right of the abscissa was taken as 0 degrees and the inferior and superior directions of ordinate were + 90 or − 90 degrees respectively

For statistical treatment of angular data the procedure suggested by Downs and associates[11] was used Among other advantages this method avoids difficulties inherent to the numerical discontinuity point at ± 180 degrees. The prevalent direction (Å) of each timed vector is determined An index d which varies from 0 to 1 measures the precision of the prevalent direction The closer its value approaches 1 the greater is the cluster of

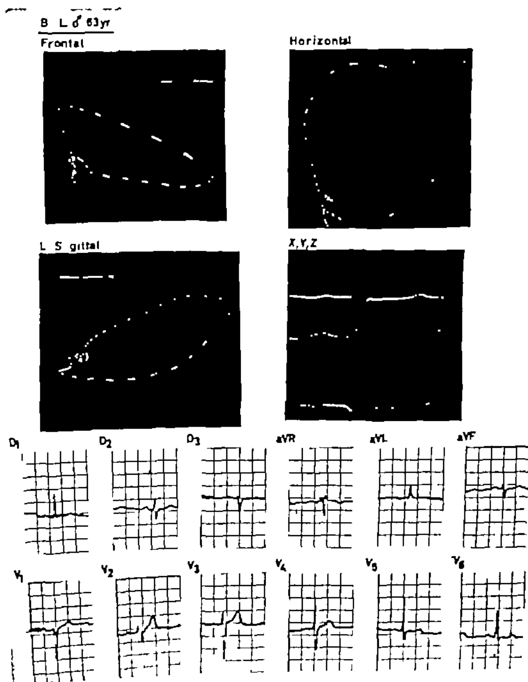


Fig 1 Electrocardiogram and vectorcardiogram of a 63-year-old man with atherosclerotic angina pectoris, and peripheral vascular disease. Calibration 500 µv The loop is interrupted every 1/400 sec.

the angles. Furthermore, to take into account the size of the sample, a χ^2/df value is calculated and indicates the significance of clustering. If χ^2/df is greater than 3.00, 4.61, or 6.91, the clustering is significant at the 5, 1, or 1 per cent level, respectively.

Description of patients

The following electrocardiographic criteria were used for selection of the patients: (1) total QRS duration shorter than 120 msec. (2) deviation of the mean QRS axis to the left and superior of −30 degrees in the frontal plane (3) ventricular complexes showing a tall R wave in Leads I and aV and an rS morphology in Leads II, III, and aV.

The present series consists of 40 patients (25 male, 15 female) ranging in age from 45 to 82 years with an average of 61. They were clinically evaluated in our department and the following clinical features were disclosed: arterial hypertension with diastolic pressure higher than 100 mm. Hg (23 cases), atherosclerosis with calcifications of the ascending aorta (21 cases), radiologic evidence of left ventricular hypertrophy (20 cases), peripheral vascular disease (15 cases), angina pectoris (9 cases), aortic valvular disease (2 cases), and mild mitral incompetence probably related to papillary muscle dysfunction (2 cases). No patient with pulmonary emphysema or chronic lung disease was included in the present group.

Results

The total duration of the QRS complex was 92.5 msec. ± 12.4.

Three main inflection points (Figs. 1, 2, and 5) were consistently observed in the loops. On the average, they occurred at 15 msec. (10 to 20), 35 msec. (30 to 40), and 65 msec. (50 to 70), respectively. The

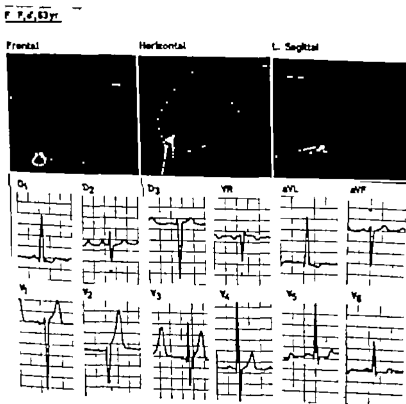
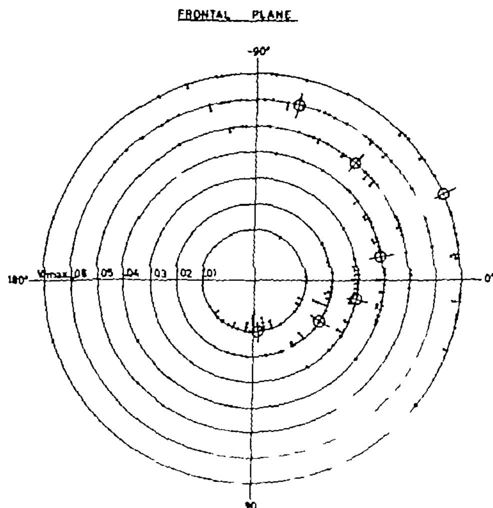


Fig. 2. Electrocardiogram and vectorcardiogram of 63-year-old man with aortic stenosis and mild mitral regurgitation. These tracings were recorded on the same day as the second electrocardiogram of Fig. 8. Calibration 500 µv. The loop is interrupted every 1/200 sec.

loop was thus divided into four parts which for description purposes have been designated as initial early midtemporal and late portions of the QRS [14]

The frontal plane loop was open faced and inscribed counterclockwise in all cases. The initial vectors were nearly always directed inferiorly either to the right or to the left. The efferent limb proceeded horizontally to the left Between 30 and 40 msec the loop abruptly swung superiorly and the midtemporal vectors were inscribed in the left superior quadrant. The third inflection point was located at about −90 degrees. Therefrom the return to the E point was achieved with small delay if any The loop passed a little into the right superior quadrant in 14 cases. In 26 patients 9 of whom had left ventricular hypertrophy the shape of the frontal plane loop was nearly that of a right angled triangle (Fig 1)

The remaining 14 patients (11 of whom had left ventricular hypertrophy) showed a more circular frontal loop (Fig 2) with a midtemporal portion of the QRS bending



	0.01 sec	0.02 sec	0.03 sec	0.04 sec	0.05 sec	0.06 sec	Vmax
Â	66	32	11	11°	50°	77	25
d	0.70	0.81	0.96	0.90	0.85	0.82	0.77
χ^2/df	18.71	26.57	36.63	32.4	28.9	26.89	23.59

Fig 3 Scattergram of the angular direction of the maximal and t ntaneous t ied ectors the frontal plane. The prevalent direction (Â) is indicated by the ign ♠. See text for definition of d nd χ^2/df

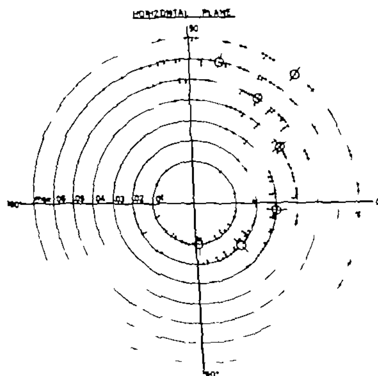
outward. The incidence of this type of vectorcardiogram was significantly higher in the presence of left ventricular hypertrophy as judged from chest films ($p < 0.01$).

The maximal frontal vector occurred at 45 msec. (± 12) and its mean voltage was 1.56 mv ± 0.67. The scattergram and statistical analysis of the 40 patients' tracings indicated a good degree of clustering for each timed vectors in the frontal projection (Fig. 3).

The horizontal plane loop was inscribed counterclockwise in all cases. The initial vectors were directed anteriorly in all but 3 patients, 3 of whom exhibited advanced left ventricular hypertrophy. The loop soon moved posteriorly and occupied the left posterior quadrant. The late portion proceeded nearly along the Z axis with minimal crossing to the right in 14 instances. The maximal vector occurred at 48 msec. ± 10 and its mean voltage was 1.84 mv ± 0.82.

Statistical analysis of the 40 tracings indicated that, the 10 msec. vectors being excepted, the instantaneous and maximal vectors were very clustered in the horizontal plane (Fig. 4).

The left sagittal plane loop showed characteristic alterations (Fig. 5). It was inscribed entirely or mostly counterclockwise in all but 5 patients. The initial vectors were nearly always directed anteriorly and inferiorly and the loop soon passed behind the Y axis. At about 30 to 40 msec.



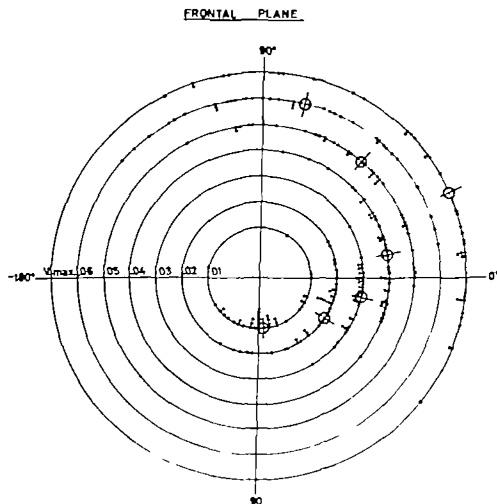
	0.01 sec	0.02 sec	0.03 sec	0.04 sec	0.05 sec	0.06 sec	max
↑	87°	44	5	33°	57°	6°	5
	0.34	0.72	0.104	0.87	0.9	0.92	0.82
χ^2 (df)	13	23.88	27.96	30.7	32.24	34.18	26

Fig. 4. Scattergram of the angular direction of the maximal and instantaneous timed vectors in the horizontal plane.

loop was thus divided into four parts which for description purposes have been designated as initial early midtemporal and late portions of the QRS [14]

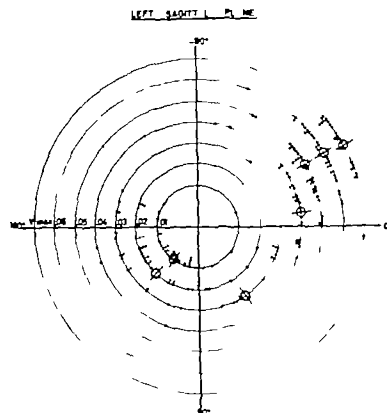
The frontal plane loop was open faced and inscribed counterclockwise in all cases The initial vectors were nearly always directed inferiorly either to the right or to the left. The efferent limb proceeded horizontally to the left. Between 30 and 40 msec the loop abruptly swang superiorly and the midtemporal vectors were inscribed in the left superior quadrant. The third inflection point was located at about −90 degrees Therefrom the return to the E point was achieved with small delay if any The loop passed a little into the right superior quadrant in 14 cases. In 26 patients 9 of whom had left ventricular hypertrophy the shape of the frontal plane loop was nearly that of a right angled triangle (Fig 1)

The remaining 14 patients (11 of whom had left ventricular hypertrophy) showed a more circular frontal loop (Fig 2) with a midtemporal portion of the QRS bending



	0.01 sec	0.02 sec	0.03 sec	0.04 sec	0.05 sec	0.06 sec	Vma
Â	86	32	11	11°	50°	77	25
ϕ	0.70	0.81	0.96	0.90	0.85	0.82	0.77
χ^2/df	19.71	26.57	36.63	32.4	28.9	26.89	23.59

Fig 3 Scattergram of the angular direction of the maximal and instantaneous timed vectors in the frontal plane. The prevalent direction (Â) indicated by the sign ϕ. See text for definition of d and χ^2/df



	0.01 sec	0.02 sec	0.03 sec	0.04 sec	0.05 sec	0.06 sec	Vmax
x̄	127°	113°	58	8°	30°	30	28°
	0.71	0.81	0.30	0.46	0.81	0.85	0.85
σ	20.16	14.66	16	17.4	15.12	15.08	16.10

Fig. 6. Scattergram of the angular direction of the maximal and instantaneous timed vectors in the left sagittal plane.

the anterior division of the left branch during transventricular mitral or aortic commissurotomy[11] or during corrective incision of the left ventricular outflow tract in patients with idiopathic hypertrophic subaortic stenosis.

Observations derived from direct epicardial recordings indicate the following pattern of excitation in experimental left anterior arborization block. The earliest focus of epicardial depolarization is located near the anterior trabeculated zone of the right ventricle about halfway to the apex (15 to 20 msec.). Depolarization of the epicardial surface of the posterior portion of the left ventricle occurs between 30 and 40 msec. and the activation is much delayed in the laterobasal region of the left ventricle where excitation occurs between 50 and 70 msec.

It seems very tempting to interpret our findings in the light of these experimental results. The initial anterior vectors of our cases would mainly represent the activation of septal and paraseptal masses. The early vectors horizontally directed to the left and posteriorly would be predominantly determined by the spread of activation into the posterodiaphragmatic portion of the left ventricular free wall. Finally the midtemporal vectors located in the left posterior and superior octant would result from markedly delayed excitation of the laterobasal wall of the left ventricle.

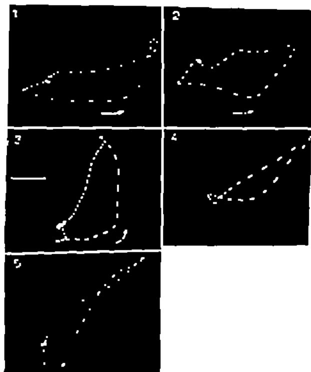


Fig 5 Examples of isolated sagittal plane loops showing the QRS loop and its four separate portions. In Cases 1 2 3 and 4 the posteriorly directed movement of the early vectors is seen as a straight, easily identified segment. In Case 5 this movement is smaller and most of the early vectors are inscribed almost perpendicularly to the sagittal plane.

there was a rapid movement directed superiorly and the midtemporal vectors were inscribed in the posterosuperior quadrant. The loop was elongated Its maximal vector occurred at 55 msec ± 8 was located at about −30 degrees and had a mean voltage of 1 84 mv ± 0 66

It should be noted that the posteriorly directed movement of the early portion of the loop varied in amplitude In the majority of cases the early vectors constituted an easily identified horizontal straight segment (Fig 5 parts 1 through 4) but in some instances the posterior displacement was smaller and most of the corresponding vectors were inscribed almost perpendicularly to the sagittal plane (Fig 5 part 5) This feature accounts for the considerable scatter observed at 30 msec in this projection while there was reasonably good cluster at 10 and 40 msec and extremely good cluster at 50 and 60 msec (Fig 6)

In summary the important diagnostic features of these vectorcardiograms include (1) initial vectors of ventricular depolarization directed anteriorly and inferiorly in most instances (2) early vectors traveling horizontally to the left and to a variable extent posteriorly (3) abrupt upward shift of the loop between 30 and 40 msec. and midtemporal vectors located in the left superior and posterior octant.

In 5 patients although the standard electrocardiograms fulfilled all the selection criteria the vectorcardiograms did not exhibit the characteristic features that have just been described On the contrary the rotation was entirely clockwise in the left sagittal projection and the early electromotive forces were directed anteriorly (Fig 7)

Finally the following clinical observations deserve being reported (1) three patients whose electrocardiograms initially showed a left axis deviation with a RI rSIII pattern subsequently developed a complete left bundle branch block (2) the characteristic electrocardiographic and vectorcardiographic features considered in this paper were sometimes observed to be intermittent (2 cases) or transitory (3 cases) They suddenly appeared for instance during an exercise test in 2 patients with angina pectoris Fig 8 illustrates a case of transitory left axis deviation In this 63-year-old patient with congenital aortic stenosis we observed several abrupt shifts from normal QRS axis to left axis deviation These changes took place without any attending clinical event Furthermore whenever left axis deviation developed it was accompanied by inversion of the T wave in Leads I and aVL The T wave alteration most likely secondary to change in ventricular excitation mimicked the so-called pattern of left ventricular hypertrophy with strain

Discussion

Production of a septal laceration which interrupts the anterior rami of the left bundle branch in the baboon heart is attended by changes in the spread of activation into the anterior free wall of the left ventricle [8] The electrocardiographic expression of these changes is a leftward shift of the mean QRS axis to −30 degrees or higher Similar observations have been reported in man after surgical injury to

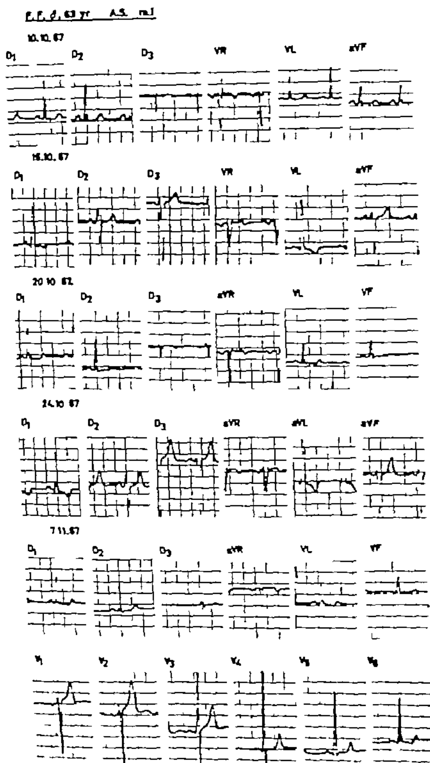


Fig. 4 Same patient as in Fig. 2. These five electrocardiograms were recorded a few days apart. The second and fourth tracings show left axis deviation with an inverted T wave in Leads I and V_6. The precordial leads of the last tracing are shown to allow comparison with those recorded in the presence of left axis deviation (Fig. 2).

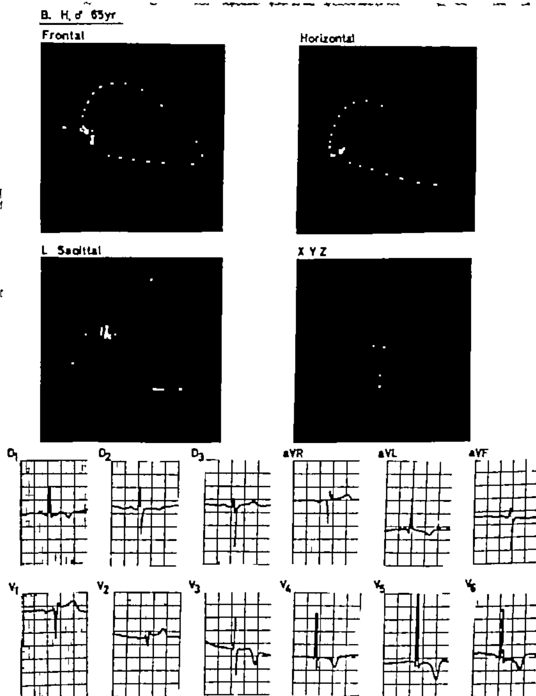


Fig 7 Electrocardiogram and vectorcardiogram of a 65-year-old man with ischemic heart disease and mild hypertension. Calibration 500 µv The loop is interrupted every 1/400 sec To be noted, the anterior localization of the initial and early vectors and the clockwise rotation of the sagittal plane loop

The following observation might also support the latter assumption From comparison between epicardial excitation maps and vectorcardiograms recorded in the same patients Arntzenius[17,18] has recently showed that the main inflection points of the QRS loop reflect major occurrences in the excitation of the heart. In particular the inflection points where the loop changes first from an anterior to posterior direction and later from a leftward to rightward direction were found to coincide with the breakthrough of the excitation fronts at the right anterior and left ventricular epicardium respectively Since epicardial recordings were not available in our series we could only try to draw a parallel between our vectorcardiogram findings

pattern of left ventricular hypertrophy with left axis deviation may be a transitory phenomenon. This feature already reported by Segers and associates[a] in 1952 supports Pruitt's opinion[a] that both the abnormal direction of activation and some of the evidence of LVH might be due to conduction disturbances.

Five patients of the present series showed anteriorly oriented initial and early electromotive forces, and an entirely clockwise rotation of the left sagittal plane loop. These cases would take place in type II of Testoni's classification.[a] The pathologic differences that could account for the peculiarities of those 5 tracings are unknown and deserve further study. Testoni[10] assumes that the causative factor might be pathologic alterations involving the posteroseptal area or the posteroinferior wall of the left ventricle. This interpretation is admittedly purely speculative and its substantiation must await histologic proof.

Summary

The authors have studied the vectorcardiograms of 40 patients, 45 years of age or over, whose electrocardiograms showed a QRS duration shorter than 120 msec., a leftward shift of the mean QRS axis and ventricular complexes with a tall R wave in Leads I and aVL, and an rS morphology in Leads II, III, and aVF.

Most patients had atherosclerous hypertension, or ischemic heart disease.

The following vectorcardiographic characteristics were disclosed: (1) The frontal plane loop was open-faced and turned counterclockwise in all cases. (2) the initial vectors were nearly always directed anteriorly and inferiorly. (3) the early vectors travelled horizontally to the left and, to a variable extent, posteriorly. (4) the mid temporal vectors were located in the left posterior and superior octant.

These vectorcardiographic features were sometimes observed to be transitory or intermittent or to precede the development of a complete left bundle branch block. Their association with a complete right bundle branch block is known to be a common forerunner of complete atrioventricular block.

From comparison with experimental data reported in the literature, the characters of the loops observed in these cases are assumed to be related to a delayed activation of the anterolateral wall of the left ventricle and to correspond to left anterior focal block.

We would like to sincerely thank Professor A. Nizet for his most helpful interest and for the opportunity to perform this study in his department.

We also wish to thank Miss S. Smeets and Mrs. B. Verver for their technical and secretarial assistance.

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and the epicardial data obtained in the primate heart after production of a left anterior arborization block It is worth being noted that there is indeed a very satisfactory correlation in timing between the three successive inflection points seen in the vectorcardiograms of our patients and the arrival of excitation at the epicardial surface of the anterior left posterior and left laterobasal aspects of the primate heart in the presence of experimental left anterior arborization block

According to these data and although no pathologic or electrophysiologic data were actually obtained in our patients it is assumed that the type of vectorcardiograms described in this paper corresponds to a left anterior focal block. The same opinion has been expressed by Testoni and associates[10] who studied various forms of focal blocks and by Cohen and coworkers[19] who observed vectorcardiograms exactly similar to ours in cases where aberrant ventricular conduction was experimentally produced by introduction of atrial premature beats

The observations that the electrocardiographic and vectorcardiographic patterns described here may be transitory or intermittent,[16 19,24] that they may precede complete left bundle branch block and finally that their association with right bundle branch block is a common forerunner of complete atrioventricular block[21 26] represents further pieces of evidence to support the hypothesis according to which this type of left axis deviation are related to a focal conduction disturbance of the left bundle branch

The pathologic basis of these vectorcardiographic changes are not yet precisely known They undoubtedly may vary in both location and extent.[21 26] This assumption is substantiated by the experimental demonstration that the same axis shift may be obtained either by a proximal block (septal laceration)[7 8] or by a distal block (cocaine solution injection into the left ventricular free wall) [8]

Similarly in man the anterior radiation of the left bundle branch may be proximally interrupted in the interventricular septum either by surgical injury [4 13 8] infarction [17] or fibrotic infiltration [1-4 8] The latter process seems rather frequent after 50 years of age. It is known that fibrosis, hyalinization with or without calcification of the mitral valve the pars membranacea, the central fibrous body and/or the summit of the muscular ventricular septum may be observed in most hearts in the fifth and sixth decades [25-30] This sclerosis of the left side of the cardiac skeleton which seems particularly frequent in hypertension and coronary heart disease[30] may catch the adjacent left bundle branch or its major ramifications.[21,28-30]

In some autopsied cases of left axis deviation histological examination of the heart revealed fibrotic lesions involving predominantly the fibers of the anterior division [4 8] In other instances the whole left bundle branch appeared extensively involved [21 26] In the latter cases it is most likely that a few undamaged specific fibers are sufficient to conduct the activation from the node to the left ventricle and that the anterior division of the left bundle has a greater conduction delay than that of the posterior ramification

On the other hand a significant number of hearts from patients with left axis deviation exhibit on serial sectioning no anatomic abnormalities of the proximal portions of the conduction system [4,26,31] In those patients, the conduction delay probably results from diffuse or scattered myocardial lesions.

Variations in the location of the lesions producing the block might account for the scatter of the initial vectors. To be noted that in 5 cases of the present series the initial vectors start posteriorly This sign usually suggests an anteroseptal infarction[32] but is no longer reliable in the presence of advanced left ventricular hypertrophy [33,34]

The present observations also confirm that a left anterior focal block is frequently associated with left ventricular hypertrophy (50 per cent of our cases) The presence of LVH results in changes in magnitude but not in direction of the instantaneous vectors and the loop maintains all its essential characteristics. It is likely that the left axis deviation is not due to LVH alone but suggests a conduction delay in addition [1] The case illustrated in Fig 8 is particularly interesting in that respect and shows that the electric

The effect of acute thermal stress on general and pulmonary hemodynamics in the cardiac patient

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Interest in the relation between heat stress and the circulation was recognized as early as 1889 when Mosso[1] observed an increase in cutaneous circulation in the limbs secondary to raising environmental temperature For the next few decades works were mainly concerned with the effect of heat on the circulation in the extremities.[2-4] Later on interest was extended to the effect of acute thermal stress on the general hemodynamics and with the advent of cardiac catheterization organized studies including pulmonary hemodynamics were also made possible

On the other hand interest in the hazards of acute thermal stress on cardiac patients started much later Berenson and Burch[5] were the first to observe aggravation of the symptoms of heart failure on elevation of atmospheric temperature and humidity Later on Burch and DePasquale[6] commented on the beneficial effect of air conditioning on hospitalized cardiac patients

However while studies on the effect of heat in normal subjects are not uncommon, such studies in cardiac patients are rather sparse[11] This may be in itself a fair reflection of the hazards of acute thermal stress on the cardiac patient. On the other hand there is no agreement as to the extent and methodology utilized in experiments of acute thermal stress by various workers. These would differ for example from a short-term exposure to a dry warm atmosphere on one hand—(which in fact, constitutes no heat stress, but rather a trial to design an artificial atmospheric situation with a claimed therapeutic value in some cardiac patients[11]) to the creation of a decisively stressful situation where the ambient temperature is raised to 43° C with a relative humidity of 85 per cent[12] on the other These may explain the controversial results and would certainly limit the exchange of data.

The thermal stress applied in the present work was planned to raise the ambient temperature from 22 ± 1 C to a relatively high degree (40 ± 1 C) while keeping a constant degree of relative humidity of 65 ± 3 per cent This made it possible to prolong the experiment for two hours while minimizing the hazards of the thermal stress particularly on cardiac patients. On the other hand the artificially induced

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The effect of acute thermal stress on general and pulmonary hemodynamics in the cardiac patient

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The thermal stress applied in the present work was planned to raise the ambient temperature from 22 ± 1 C to a relatively high degree (40 ± 1 C) while keeping a constant degree of relative humidity of 65 ± 5 per cent. This made it possible to prolong the experiment for two hours, while minimizing the hazards of the thermal stress particularly on cardiac patients. On the other hand the artificially induced

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atmosphere would in our opinion simulate more closely many of the practically observed situations of acute heat stress

Material

A control group of 6 normal adults and 3 cardiac groups of 18 patients were the subjects of the study The 3 groups of cardiac patients selected were 8 patients with rheumatic mitral stenosis 6 patients with emphysema cor pulmonale and 4 patients with bilharzial cor pulmonale The selection was based on the varied pathogenesis of pulmonary hypertension in the 3 groups, giving a wider chance for the study of the effect of heat stress on different patterns of abnormal pulmonary hemodynamics

Method

The experiment was performed in the morning under basal conditions. The subjects were prepared beforehand by briefly outlining the procedure and they were given 0 1 Gm of Luminal intramuscularly a half hour before the start This helped to allay the patient s apprehension

Venous catheterization was performed through a left antecubital vein The catheter was advanced to the main pulmonary artery and an indwelling Cournand arterial needle was inserted in the femoral artery The patient was left until a steady pulse rate was achieved then a Jones-Air Basal basal metabolic rate apparatus was applied to determine the O_2 consumption. At the middle of rebreathing through the apparatus a simultaneous mixed venous sample from the pulmonary artery and arterial sample from the femoral artery were taken anaerobically by a syringe containing 0 1 ml of heparin (5 000 U.S.P U per milliliter)

After completion of the O_2 consumption determination the pulmonary artery pressure and its mean value were recorded the catheter was withdrawn to the right ventricle and atrium their corresponding pressures being recorded meanwhile The catheter was then advanced to a wedge position the wedge and mean wedge pressure recorded and the catheter left in situ The catheter was kept patent by continuous infusion of heparinized 5 per cent glucose drip at the rate of 30 drops per minute Blood pressure rectal temperature and 14 lead electrocardiograms (ECG s) were obtained (adding V_{4R} and V_{3R} to the conventional leads)

Then the heating procedure was started by heaters arranged in the catheterization room The temperature of the air could thus be raised up to 40 ± 1 C within 15 to 20 minutes The duration of heat exposure was 2 hours starting from the

Table I

Group	*Rectal temperature (degrees C)*			*Oxygen consumption (ml /min /M)*			*Respiratory rate (cycle/min)*		
	Befor heat	*After heat*	*Change (degree C)*	*Before heat*	*After heat*	*Change %*	*Before heat*	*After heat*	*Change %*
Normal	36 9	39 5	+2 6 (0 12)	179 5	241 7	+34 7 (12 43)	18 7	25 3	+35 3 (10 84)
Mitral stenosis	36 8	39 3	+2 5 (0 11)	137 1	184 5	+34 6 (7 8)	22 9	40 0	+74 7 (27 2)
Emphysema cor pulmonale	36 7	39 1	+2 4 (0 11)	134 3	188 5	+40 4 (10)	21 7	33 2	+53 0 (22)
Bilharzial cor pulmonale	36 7	39 1	+2 4 (0 12)	174 8	231 3	+32 0 (8 3)	15 5	21 75	+40 3 (6 5)

Standard deviation in parentheses.

moment the temperature reached the required level. The humidity of the air was measured by a hair hygrometer which denoted directly the relative humidity

At the end of the 2 hours exposure to heat, the same parameters were measured as before heating

Heart rate was calculated from the ECG tracing recorded simultaneously with the pressure tracings. Arterial blood pressure was measured by mercury sphygmomanometer. Rectal temperature was measured by a clinical thermometer. The ECG was recorded by a 4 channel Elema Schönander Mingograph. Intracardiac pressure was measured by an Elema Schönander transducer-electromanometer recorder set, by which the systolic diastolic, and mean pressures can be read directly (zero level 10 cm above the back). Oxygen saturation in blood samples was estimated photoelectrically by an Elema Schönander AB oximeter. Cardiac output was calculated by the direct Fick's principle, resistances and ventricular work were calculated according to Gorlin's formulas.[14,3]

Results

The results are listed in Tables I, II and III. Table I shows changes in rectal temperature, oxygen consumption, and blood oximetry. Table II includes changes in general hemodynamics. Table III contains changes in pulmonary hemodynamics

Discussion

The degree of acute heat exposure utilized in the present experiment resulted in a rise of rectal temperature of about 2.5° C. A similar degree of rise in body temperature was observed in both the normal and the 3 cardiac groups of patients. This is explained by the fact that the final degree of rise of body temperature depends on the augmentation of body heat production through stimulation of body chemical processes. This mechanism is essentially the same in both normal subjects and cardiac patients

Acute thermal stress resulted in augmentation of oxygen consumption, the increase of which was nearly the same in all groups (34.7, 34.6, 40.4, and 32 per cent in the normal, mitral stenosis, emphysema cor pulmonale, and bilharzial cor pulmonale groups, respectively). The increase in oxygen consumption is related to the degree of rise of rectal temperature. However, for almost the same rate of increase of oxygen consumption, the respiratory rate increased at widely different rates (35.3, 74.7, 53, and 40.3 per cent in the normal, mitral stenosis, emphysema, cor pulmonale, and bilharzial cor pul

Arterial oxygen saturation (%)			*Central venous oxygen saturation* (%)			*Arteriovenous oxygen difference* (volume/liter)		
Before heat	After heat	Change %	Before heat	After heat	Change %	Before heat	After heat	Change %
96.7	97.7	+1 (0.94)	62.2	73.3	+17.8 (7.81)	55.2	38.6	−30.1 (8.81)
97.0	94.4	−2.7 (2.2)	55.4	63.5	+14.6 (8.8)	62.4	47.4	−24 (9.2)
82.7	86.2	+4.2 (2.6)	50.0	62.0	+24 (24.3)	48.5	37.2	−22.3 (9.4)
96.3	97.8	+1.6 (1.9)	58.8	68.8	+16.6 (5.4)	65.3	50.65	−22.4 (10.1)

Table II. Changes in general hemodynamics

Group	Cardiac output (L./min.)			Heart rate (ml./min.)		
	Before heat	After heat	Change %	Before heat	After heat	Change %
Normal	5 28	10 29	+94 9 (18 5)	74 2	123 8	+66 8 (34 2)
Mitral stenosis	3 49	6 26	+79 4 (17 2)	83 1	148 1	+78 2 (13 4)
Emphysema cor pulmonale	4 68	8 33	+78 (13 7)	80 8	132 2	63 6 (13 5)
Bilharzial cor pulmonale	4 50	7 74	+72 0 (20 4)	70 3	121 0	+72 1 (22 7)

Standard deviation in parentheses.

Table III. Pulmonary hemodynamics

Group	Mean wedge pressure (mm. Hg)			Mean pulmonary arterial pressure (mm. Hg)			Right ventricular pressure* (mm. Hg)		
	Before heat	After heat	Change	Before heat	After heat	Change	Before heat	After heat	Change %
Normal	4	5	+14 2 (9 1)	10 5	16	+52 4 (18)	21	29 5	+40 5 (18 2)
Mitral stenosis	16 8	27 6	50 5 (22 9)	37 4	50 3	+35 0 (14 4)	49	66 5	+35 7 (13 8)
Emphysema cor pulmonale	5 5	7 8	+20 1 (40 2)	28 8	38	+31 9 (13 6)	38	50 5	+32 9 (14 7)
Bilharzial cor pulmonale	5	5	0 0	35	65 5	+87 1 (29 1)	55 25	89 75	+62 4 (23)

Standard deviation in parentheses.
*Systolic pressure

monale groups respectively) The disproportionate tachypnea in patients with mitral stenosis indicates that in addition to the stimulating effect of heat on the respiratory center other factors linked to the pathologic state come into play probably reflexes from the lung secondary to the enhanced pulmonary venous congestion some patients actually entered into early grades of acute pulmonary edema

The systemic circulation showed marked changes after acute thermal stress becoming hyperkinetic in character both in the control group and in the cardiac patients. There was a consistent marked drop in

Stroke volume (ml./beat)			Total peripheral resistance (units)			Left ventricular work (Kg. M./min./M. BSA)		
Before heat	After heat	Change %	Before heat	After heat	Change %	Before heat	After heat	Change %
73 8	84 2	+14 1 (25 2)	18 7	8 4	−55 (9 0)	4 31	7 12	+65 3 (16 8)
42 5	42 3	−0 5 (15 0)	25 1	11 0	−56 2 (4 0)	2 56	3 49	+36 3 (26 3)
58 5	62 9	+7 5 (7 7)	20 6	10 15	−50 7 (3 2)	3 64	5 47	+50 3 (23 1)
61 3	65 4	+1 7 (4 7)	21 31	9 97	−53 2 (8 4)	3 45	4 70	+36 2 (10 5)

Mean right ventricular pressure (mm. Hg)			Pulmonary arterial resistance (units)			Right ventricular work (Kg. M./min./M. BSA)		
Before heat	After heat	Change	Before heat	After heat	Change %	Before heat	After heat	Change %
2	2 7	+32 2 (18 2)	1 23	1 05	−14 5 (14 8)	0 40	1 18	+197 1 (104 8)
2 3	5 0	+59 3 (47 3)	6 17	4 09	−33 7 (10 9)	1 09	2 52	+131 2 (13 3)
3 75	5 58	41 5 (32 6)	4 88	3 63	−25 6 (12 6)	1 03	2 32	+125 2 (51 7)
1 75	3 25	44 2 (39 2)	6 68	7 94	+18 9 (6 4)	1 26	4 26	+238 1 (63)

the total peripheral vascular resistance. Exposure to heat results in marked cutaneous vasodilatation involving both primary release of the vasoconstrictor tone and active vasodilatation.[19,20] The percentage of drop of the total peripheral vascular resistance under similar degrees of acute thermal stress was comparable in the normal group and in the 3 groups of cardiac patients (55, 56.2, 50.7, and 53.2 per cent in the normal, mitral stenosis, emphysema cor pulmonale, and bilharzial cor pulmonale groups, respectively) even though the initial level of the total peripheral vascular resistance may be different.

Acceleration of the circulation through the widely dilated vessels supplying the relatively metabolically inert skin to enhance heat dissipation resulted in marked changes in blood oximetry with increase in the central venous blood oxygenation and a concomitant drop in the arteriovenous oxygen difference The arterial blood oxygenation on the other hand *showed negligible changes in the normal group and in patients with bilharzial cor* pulmonale while in the mitral stenosis group it showed a slight drop explained by the enhancement of the pulmonary venous congestion and the occurrence of early grades of acute pulmonary edema in some cases Patients with emphysema cor pulmonale showed increase in arterial oxygen saturation associated with improvement and disappearance of central cyanosis in some cases.

The cardiac output showed almost twofold increase in the normal group (94 9 per cent) The increase in cardiac output in the 3 groups of cardiac patients was slightly less but comparable to each other (79 4 78 and 72 per cent in mitral stenosis, emphysema cor pulmonale and bilharzial cor pulmonale patients respectively) Cardiac output is determined by the stroke volume and heart rate The increase in cardiac output after acute thermal stress occurred mainly through augmentation of the heart rate. However in the normal group there was a slight increase in the stroke volume (14 1 per cent) In the emphysema cor pulmonale patients the increase in the stroke volume was less (7 5 per cent) On the other hand the increase in cardiac output in the mitral group and in the bilharzial cor pulmonale group was attributed solely to augmentation of the heart rate. The negligible change in the stroke volume in both groups can be explained by the restrictive nature of their hemodynamic fault.

Changes in the pulmonary *circulation* secondary to acute *thermal stress were no* less striking than those observed in the systemic circulation Insignificant changes occurred in the wedge pressure in the normal group patients with bilharzial cor pulmonale and most of the patients with emphysema *cor pulmonale*. However one patient with emphysema cor pulmonale showed a significant rise of the wedge pressure which was apparently related to the development of left ventricular decompensation secondary to the hemodynamic burden of the thermal stress. On the other hand patients with mitral stenosis showed significant increase in the wedge pressure ranging from 28 to 100 per cent of the original values. In cases *of mitral stenosis under acute thermal stress the cardiac output increased while* the diastolic filling period decreased secondary to marked increase in heart rate. Both of these changes explain the significant increase in the wedge pressure. Augmentation of heart rate is deleterious to patients with *mitral* stenosis in which the entire period of diastole is presumably taken up by inflow therefore a small increase in heart rate may exert great influence on the time available for inflow A fair degree of correlation was demonstrated between the rate of increase in the wedge pressure and the degree of augmentation of the heart rate (Fig 1) The rise in pulmonary capillary pressure may attain considerably high levels in some cases of mitral stenosis and the patients may enter into frank acute pulmonary edema. This represents one of the two main clinical

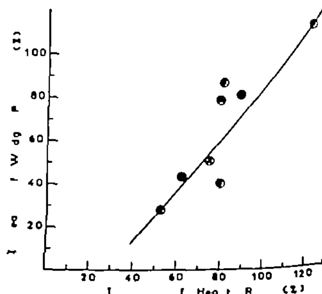


Fig 1 The relation between the degree of increase of heart rat and the rate of rise of wedge pressure after acute thermal tress n patient with mitral stenosis.

hazards of acute thermal stress on patients with mitral stenosis. The other hazard is acute right ventricular decompensation and the appearance of clinical signs of congestive heart failure.

The changes in the pulmonary arteriolar resistance secondary to acute thermal stress raise considerable interest, since the pulmonary circulation is a distensible low pressure system of vessels and therefore behaves as distensible rubber tubes through which an increase in flow would induce dilatation by increasing the transmural pressure. This means that a change in the calculated resistance does not necessarily imply the presence of active constriction or dilatation and a change can merely occur on a purely physical basis.[21] The reaction of the pulmonary vascular bed to acute thermal stress is expected to differ from the reaction of the systemic vascular bed (the structure and function of both circulations widely differ). In homoiotherms, a major task of the systemic circulation is thermoregulation which is effected through differentiation of the systemic circulation in two sites the surface and the core of the body. The surface circulation is subjected to intensive vasodilatation in order to facilitate heat dissipation to the exterior while the latter is subjected to compensatory vasoconstriction in partial compensation for the drop in vascular resistance caused by vasodilatation in surface circulation. There is no such differentiation in the pulmonary circulation and this fits with its main function in man, viz. gaseous exchange. On the other hand, while much information is available now on the regulation and adjustment of the blood flow in the systemic circulation, our knowledge about the pulmonary circulation is still incomplete. The role of active autonomic vasomotor control or passive regulation secondary to changes in systemic circulation, pulmonary blood volume, and bronchomotor tone in health and disease is still in debate.[22] In experiments of acute thermal stress, the pulmonary vascular bed facing a nearly twofold increase in heated blood flow would dilate to accomodate for this. Although part of the dilatation is passive, secondary to the increased flow, an active vasodilatation, probably the result of the direct effect of heated blood on the blood vessels, cannot be excluded. However, this decrease in pulmonary vascular resistance will be difficult to document in the normal lung compared, for example, with the changes in systemic vascular resistance, simply because of the marked difference in the normal degree of vasomotor tone in both circulations. The situation will differ in the presence of raised pulmonary arteriolar resistance; the pulmonary vascular bed will acquire similar characteristics to the systemic

Table IV. Changes in pulmonary artery/wedge pressure gradient and pulmonary blood flow in response to acute heart stress in cases of mitral stenosis

Case	Mean pulmonary arterial pressure/mean pulmonary capillary venous pressure gradient (mm. Hg)			Pulmonary blood flow (L./min.)		
	Before heat	*After heat*	*Change %*	*Before heat*	*After heat*	*Change %*
7	26	33	+27	2.75	5.32	+ 93
8	18	18	0	3.96	6.33	+ 60
9	22	24	+ 6	3.00	4.83	+ 61
10	22	24	+ 9	3.17	5.50	+ 73
11	20	24	+20	4.00	6.67	+ 68
12	10	10	0	4.00	8.00	+100
13	30	30	0	3.00	6.00	+100
14	7	8	+14	4.00	7.40	+ 85

vascular bed and the pulmonary arteriolar resistance may sometimes approach the systemic resistance However the response of the pulmonary vascular bed will depend primarily on the mechanism governing the raised pulmonary arteriolar resistance viz whether it is mainly caused by a functional vasospastic element or an organic obstructive or obliterative change

In patients with mitral stenosis there was ample evidence of active pulmonary vasodilatation reactionary to acute thermal stress This was documented by finding cases that showed no changes in the pressure gradient after heat while the pulmonary blood flow markedly increased (Table IV) In these patients active vasodilatation in the pulmonary vascular bed can be safely considered As a group patients with mitral stenosis showed the maximal reduction of pulmonary arteriolar resistance after acute thermal stress (33 7 per cent) These findings would suggest that a good element of the increased pulmonary arteriolar resistance in mitral stenosis is caused by reactive vasospastic changes even in cases with a high level of pulmonary hypertension The repeatedly reported observations on the effect of the operation of mitral valvotomy on the pulmonary arteriolar resistance in cases of mitral stenosis is in support of the above statement

On the other hand the drop in pulmonary arteriolar resistance in patients with emphysema cor pulmonale was less only in one case was there practically no change in the pressure gradient after heat while the cardiac output markedly increased In this case active vasodilatation in the pulmonary vascular bed should be considered In the rest of the patients there was a variable increase in the pressure gradient after heat though always less than the concomitant increase in cardiac output resulting in a consistent drop in the pulmonary arteriolar resistance These findings reflect a decreased reactivity of the pulmonary vascular bed in emphysema A similar observation was reported by Tracks and Sancetta [11] This is probably explained by the fact that although pulmonary hypertension may be a transient factor in emphysema associated with attacks of asthma bronchitis, or pneumonia where it is due to vasoconstriction induced by acute hypoxia [22] in more advanced cases of obstructive emphysema, pulmonary hypertension is more permanently present independent of hypoxia. This type of pulmonary hypertension which can be called the obliterative type is thought to result from destruction of capillaries and arterioles in the lungs and from associated diffuse interstitial pulmonary fibrosis.[23]

Cases of bilharzial cor pulmonale showed exceptional increase in the pulmonary arteriolar resistance (18 9 per cent on the average) This is in favor of a fixed arteriolar vascular bed in which the pulmonary arterioles have practically lost their reactivity This would document the views that pulmonary hypertension in bilharzial cor pulmonale is purely of obstructive nature [24]

Information concerning the immediate relation between pressure and flow in the human pulmonary circulation comes essentially from two types of experiments the first is the effect of exercise and the second is the effect of unilateral pulmonary artery occlusion Experiments of acute heat stress can be regarded as a third tool for the study of pressure-flow relationship in the pulmonary circulation However it resembles more the effect of exercise rather than unilateral pulmonary artery occlusion in regard to the large number of variable parameters other than increased blood flow which would affect the pulmonary arterial pressure In the present experiment changes in the pulmonary arterial pressure reflected the combined changes in the wedge pressure pulmonary blood flow and the pulmonary arteriolar resistance Thus the maximal increase in pulmonary arterial pressure after acute thermal stress was observed in cases of bilharzial cor pulmonale (87 1 per cent) (Fig 2) where there was increase in pulmonary arteriolar resistance while in patients with emphysema cor pulmonale and mitral stenosis the rise in pulmonary arterial pressure was much less (31 9 and 35 per cent respectively)

In the normal subjects there was a 52 4

per cent increase in the pulmonary arterial pressure while the pulmonary blood flow nearly doubled and the wedge pressure showed insignificant changes. This relatively high increase in the pulmonary artery pressure in the normal subject upon increasing the pulmonary blood flow twofold differs from the statement advanced by Cournand[22] that no significant increase of the pulmonary arterial pressure occurs until the cardiac output exceeds the resting level by 2.5 to 3 times which might lead one to conclude that the pulmonary circulation is a remarkably distensible system. However it has since been observed that the distensibility of the pulmonary vessels which underlies this statement,[23] is a condition which needs months or years to develop and the situation is not comparable to the immediate effects which a change in flow has on the pressure in the pulmonary circulation.[22] The same thing has been observed in experiments of unilateral pulmonary artery occlusion which leads to sudden doubling of the pulmonary blood flow. In such studies, a 30 per cent increase of pulmonary arterial pressure has been reported.[24]

The effect of the hemodynamic burden of acute thermal stress on the work of the left and right ventricles is quite different. Although both left and right ventricles under the effect of acute thermal stress pump double the resting output per minute in the normal group and slightly less than that in the cardiac groups (72 to 79.4 per cent) while the left ventricle does this in the face of a reduced mean systemic arterial pressure the right ventricle has to overcome the added factor of a raised mean arterial blood pressure. Therefore the percentage of increase in left ventricular work is much less than that sustained by the right ventricle. In the present experiment the left ventricular work showed an average increase ranging from 36 to 65.3 per cent which is explained by the greater increase in the cardiac index than a concomitant lesser reduction in the mean systemic arterial pressure.

The work of the right ventricle markedly increased after acute thermal stress. In the groups of mitral stenosis and emphysema cor pulmonale the increase averaged 131.2 and 125.2 respectively. This resulted from concomitant increase in both the cardiac index and mean pulmonary arterial pressure. The work load imposed by acute thermal stress appears to be the main factor responsible for the eventual

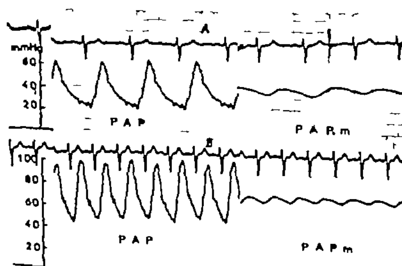


Fig. 2. Pulmonary artery pressure tracing in case of bilharzial cor pulmonale. A. Before heat. B. After heat. P.A.P. Pulmonary artery pressure in mm. Hg. P.A.P.m. mean pulmonary artery pressure in mm. Hg. The after heat tracing demonstrates mechanical alternans.

right ventricular decompensation that was observed to occur in some of the patients in both groups This was evidenced hemodynamically by a rise in the end-diastolic pressure of the right ventricle and mean right arterial pressure and clinically by the appearance of signs of right-sided heart failure Although the percentage of increase in the right ventricular work in the normal group (197 1 per cent) is higher than that in the groups with mitral stenosis and emphysema cor pulmonale the magnitude of the increase in work was less (0 78 1 43 and 1 29 Kg M per minute per square meter of body surface area in the normal mitral stenosis and emphysema cor pulmonale groups respectively)

The highest percentage of increase of the right ventricular work after acute thermal stress was observed in the patients with bilharzial cor pulmonale (238 1 per cent) This is related mainly to the considerable increase in the mean pulmonary arterial pressure which is the reflection of the obstructive nature of the pulmonary hypertension in this disease It was noted that the work load sustained by the right ventricle in patients with bilharzial cor pulmonale after acute thermal stress (average 4 26 Kg M /min /M² BSA) was nearly

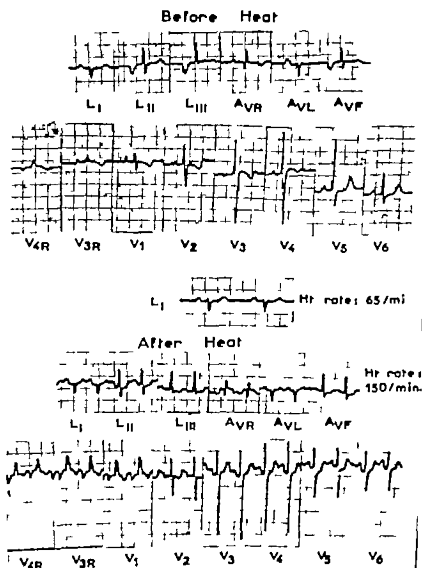


Fig 3 Electrocardiographic record of a patient with mitral stenosis before and after acute thermal stress. The R wave increased in height in V_{4R} to V the S wave increased in depth in V and V the T wave became positive in V_1 and coronary sinus rhythm disappeared after heat with the occurrence of sinus tachycardia.

double the work load sustained by the right ventricle in patients with mitral stenosis and emphysema cor pulmonale (2 52 and 2.32 kg M./mm./M BSA respectively) However it was observed that this amount of work load in the latter two groups was sufficient to lead to right ventricular decompensation in some cases, while double this load was sustained by the right ventricle in the bilharzial cor pulmonale group without hemodynamic evidence of decompensation. This interesting observation stresses the importance of the myocardial factor in the pathogenesis of cardiac decompensation in the mitral stenosis and emphysema cor pulmonale groups which is not present in patients with bilharzial cor pulmonale In fact, it is observed clinically that cases of bilharzial cor pulmonale show right ventricular decompensation as a late and terminal complication while cases of mitral stenosis and emphysema cor pulmonale usually sustain recurrent episodes of right-sided decompensation for a considerable period

In the present experiment, no significant changes in electrocardiography were observed in the normal and bilharzial cor pulmonale groups, apart from sinus tachycardia with apparent S-T-segment depression In the groups with mitral stenosis and emphysema cor pulmonale there was

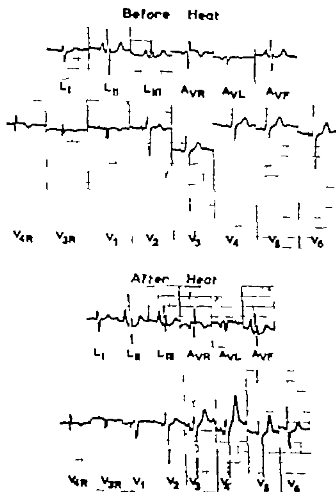


Fig 4 Electrocardiographic record of patient ith emphysema cor pulmonale before and after acute thermal stress. The after heat tracing show ncrease the height of P w vs in Leads II III and V

an increase in the right axis deviation of the mean frontal QRS vector and a shift of the terminal QRS vector in the horizontal plane to the right and anterior making the precordial leads more consistent with a right ventricular hypertrophy pattern (Fig 3) Lesser changes were observed in the degree of S-T-segment depression and T wave inversion in the precordial leads. These changes can be taken in favor of the cause and effect relationship between the hemodynamic burden of acute thermal stress and the electrocardiographic changes observed However in patients with emphysema cor pulmonale changes in the respiratory mechanics and lung volumes following the acute thermal stress may have a significant role in the genesis of the postexposure ECG

Evident changes were observed in the P wave in patients with emphysema cor pulmonale after acute thermal stress (Fig 4) The magnitude of the mean instantaneous P vector in the frontal plane was increased and the average direction tended to be more inferior and less to the left This leads to increase in the height of the P wave in Leads II III and aV_F Though the exact mechanism responsible for the P pulmonale pattern remains in debate[17] the relative importance of the hemodynamic burden of acute thermal stress in the genesis of the P wave changes can be suggested since a rough relationship could be found between the rise of the end diastolic pressure of the right ventricle and the mean right atrial pressure and the occurrence of P wave changes

Summary and conclusions

The effect of acute exposure to high environmental temperature of 40° C and 65 per cent relative humidity for 2 hours was studied in 4 groups of subjects a control group consisting of 6 normal adults and 3 cardiac groups including 8 patients with mitral stenosis 6 patients with emphysema cor pulmonale and 4 patients with advanced bilharzial cor pulmonale

Changes in the following parameters were the subject of study rectal temperature blood oximetry cardiac output arterial blood pressure peripheral vascular resistance pulmonary arterial wedge pressure pulmonary artery pressure right ventricle and right atrium pressures, pulmonary arteriolar resistance ventricular work and the ECG

From this study the following points are stressed

1 Acute thermal stress is hazardous to cardiac patients within the groups studied Mitral stenosis patients are liable to enter into acute pulmonary edema or right-sided heart decompensation emphysema cor pulmonale subjects are liable to enter into right sided heart decompensation and in patients with bilharzial cor pulmonale the marked increase in right ventricular work is a definite hazard although none of the cases studied entered into right-sided heart failure

2 Experimental acute thermal stress can be regarded as a third tool for the study of the pressure-flow relationship in pulmonary circulation in addition to exercise and unilateral pulmonary artery occlusion

The findings in the present experiment suggested that a good element of the increased pulmonary arteriolar resistance in mitral stenosis is vasospastic while patients with emphysema cor pulmonale demonstrate lesser reactivity of the pulmonary vascular bed and patients with bilharzial cor pulmonale showed a fixed vascular bed in which the pulmonary arterioles have practically lost their reactivity

3 An air-conditioned atmosphere is necessary for management of cardiac patients, and thorough clinical assessment of the cardiac condition of patients travelling to hot localities is recommended

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Hemodynamic changes at rest and during exercise in patients with aortic stenosis of varying severity

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The effects of exercise on circulation in patients with aortic stenosis have been reported previously[1-4] but attempts have not been made to correlate the hemodynamic abnormalities to the severity of the stenosis nor were the left ventricular pressures studied during exercise The purpose of this communication is to report the hemodynamic effects of exercise in relation to the severity of the disease in patients with pure aortic stenosis. Attempts were also made to measure the capacity for muscular work in a quantitative manner and to analyze the limiting factors of working capacity

Material

Thirty four patients were selected for this study on the basis of a diagnosis of isolated aortic stenosis (rheumatic and congenital) following cardiac catheterization Aortic root aortography* was also carried out in patients with the murmur of aortic regurgitation and only those with a slight regurgitation were included All cases have valvular stenosis except one who has membranous subvalvular stenosis. Cases of muscular subaortic or supravalvular stenosis were excluded

The material is classified into three groups according to the calculated aortic valve area index (AVAI) in square centimeters per square meter of body surface area In Group I AVAI is larger than 0 8 in Group II between 0 5 and 0 8 and in Group III less than 0 5 cm² per square meter Clinically Group I corresponds to mild stenosis Group II to moderate stenosis and Group III to severe stenosis. The age range is 10 to 59 years with the mean age being 34 The average age for Group I is 17 years for Group II 25 years, and for Group III 46 years

Procedures and methods

Physical working capacity (PWC) was determined on an electrically braked constant load bicycle ergometer[5] using the method of Sjöstrand[6] The work load was successively increased every 6 minutes with an aim to achieve a steady pulse rate of 150 per minute to 170 per minute in 3

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*This was carried out by the department of Radiology

work loads. The electrocardiogram was monitored every minute and the heart rate was calculated from it. The exercise was continued until either a pulse rate of 150 to 170 per minute was achieved or the patient was unable to exercise due to symptoms. Because of the possible risk, exercise was stopped with the appearance of anginal pain. The work intensity corresponding to the pulse rate of 170 per minute (PWC $_{170}$) was calculated using the approximate linear relationship of the work intensity and the pulse rate. The methods of catheterization of the right side of the heart using a double lumen catheter and cardiac output determination using the Fick principle were described previously in detail.[7] The left ventricle was also catheterized in all cases. In 25 patients, a transseptal puncture technique was used using a modified instrument as described previously. In 8 cases the left ventricle was catheterized from the aorta using a modified Seldinger technique. One patient was studied via transthoracic left ventricle puncture. Twenty-four patients were exercised in the supine position using the bicycle ergometer during cardiac catheterization. The electrocardiogram and pressures were continuously recorded on a photographic recorder (Mingograf) and the expired gas was collected in Douglas bags between the fourth and sixth minute of exercise with simultaneous collection of arterial and mixed venous blood. The methods of expired gas analysis and determination of oxygen uptake were the same as in a previous report.

Aortic valve area (AVAI) was calculated using the method of Gorlin and Gorlin. The mean systolic gradient was calculated from the simultaneous pressure recordings in the left ventricle and the aorta in 29 patients and the withdrawal pressure tracings in the remaining 5 patients. A planimeter was used to calculate the area of the pressure gradient and the left ventricular mean systolic pressure (LVMSP).

The left ventricular stroke work index (LVSWI) was calculated as follows: LVSWI (gmM per beat per square meter) = 13.6 × (LVMSP − LVEDP) × SI where LVEDP = left ventricular end diastolic pressure (in millimeters of Hg) and SI = stroke index (in milliliters per square meter). The left ventricular work index (LVWI) was obtained by substituting the cardiac index for the stroke index in the above formula and expressing as Kg M per minute per square meter.

Pulmonary vascular resistance (PVR) is expressed as the ratio of the mean pressure gradient (mm. Hg) across the pulmonary vascular bed and the cardiac output (liters per minute). Systemic resistance was calculated by dividing the mean aortic pressure by cardiac output. The heart volume was calculated from simultaneously exposed biplane chest x rays in prone position according to the method of Kjellberg and associates. Total hemoglobin was estimated using the carbon monoxide method of Sjöstrand.[11] The various parameters of these patients were compared to the normal values obtained in this laboratory using same methods.[11] The statistical analysis was carried out using the conventional methods,[11] and the P value of less than 0.05 was defined as significant.

Results

The mean and standard deviations of the body surface area, total hemoglobin, blood volume, heart volume, and heart

Table I. Some anthropometric data with mean values ± standard deviation

Group	No. of cases	B.S.A. (M²)	Total Hb. (Gm.)	Blood volume (L.)	Heart volume (ml.)	Heart volume / B.S.A.	AVAI (cm.²/M²)
I	7	1.58 ± 0.18	993 ± 129	4.53 ± 0.83	704 ± 162	421 ± 72	1.07 ± 0.43
II	10	1.70 ± 0.20	996 ± 138	4.61 ± 0.77	793 ± 192	451 ± 80	0.61 ± 0.07
III	17	1.78 ± 0.14	618 ± 149	4.88 ± 0.71	1147 ± 330	647 ± 286	0.38 ± 0.09

Abbreviations: B.S.A., body surface area; Hb., hemoglobin; AVAI, aortic valve area index.

volume per square meter of body surface are listed in Table I The total amount of hemoglobin per kilogram of body weight is 9 6 Gm in Groups I and II and 9 4 Gm in Group III the difference being insignificant The average blood volume per kilogram of body weight is 75 4 ml in Groups I and II and 73 5 ml in Group III The blood volume and the total hemoglobin per kilogram of body weight are not different from the normal individuals [7, 12]

The heart volume (HV) in prone position was measured in 32 cases and compared to the normal individuals with respect to the total hemoglobin [7, 12] In all patients with severe stenosis (Group III) the heart volume is above one standard error of estimate whereas in all patients with mild stenosis (Group I) it is within two standard errors of estimate (Fig 1) The mean heart volume index (milliliters per square meter) was 50 per cent larger in Group III compared to Groups I or II A slight (7 per cent) but significant difference was also found between I and II

All patients were exercised in attempts to estimate the work capacity at the pulse rate of 170 per minute (PWC_{170}) No symptoms were experienced by the 9 patients with mild stenosis (Group I) The average highest pulse obtained in this group was 169 per minute Two of the eight patients of Group II developed symptoms during exercise one complained of a slight chest pain and the other of general fatigue The average highest pulse rate obtained in this group was 160 per minute However all patients except one in Group III developed symptoms during exercise (chest pain in 8 and dyspnea and/or fatigue in 5) The average peak pulse for this group was 133 per minute. Thus in 13 patients of Group III the PWC_{170} could not be estimated due to symptoms In normal individuals[7, 12] and athletes[14] a close correlation exists between the working capacity (PWC_{170}) and the total hemoglobin or heart volume Thus using these normal regressions a normal work capacity can be predicted In only 2 of the 14 pa

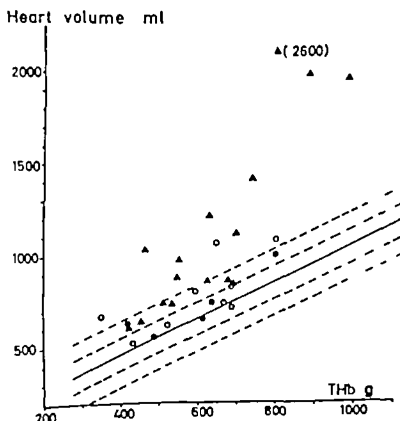


Fig *1* Correlation between heart volume and total amount of hemoglobin (*T Hb*). The continuous line indicates the normal regression and the broken lines = one and two standard errors of estimate [12] ○ = Group I ● = Group II ▲ = Group III

tents in Groups I and II the PWC_{170} was below 70 per cent of the predicted value. Similarly in only 3 of the 14 patients, the PWC_{170} was below the two standard errors of estimate according to their heart volumes.

Aortic valve area index (AVAI) varied from 1.64 to 0.21 cm.[2] per square meter. The mean value and the standard deviation is listed in Table I.

Basal oxygen consumption (VO_2) was measured using a Krogh spirometer a few days before cardiac catheterization. The predicted mean value according to Harris and Benedict is 212 ml. of STPD per minute and the actual value obtained is 226 ml. of STPD per minute. The difference is not significant. Resting VO_2 during catheterization was 24 per cent higher than the basal VO_2 obtained. The difference is similar to the results found in other patients in this laboratory.

Cardiac output and other data obtained by cardiac catheterization are presented in Table II. Cardiac output was measured in all at rest and in 24 patients during exercise (Fig. 2). In comparison to the normal values established in this laboratory, the resting cardiac output is abnormally low for the VO_2 in 3 patients of Group III but in no patient was abnormally high cardiac output found.

The cardiac index is compared to the normal material in Table III. The mean cardiac index of Groups I and II is not different from the normal values, whereas it is significantly low in Group III ($p < 0.001$). During exercise cardiac output failed to rise normally in 8 patients (Fig. 2). Consequently arteriovenous oxygen difference is abnormally increased in these patients. Seven of these 8 patients belong to Group III.

The mean arteriovenous oxygen difference at rest is significantly increased in Group III (mean = 51 ml. per liter, S.D. = ± 19, n = 14) compared to the normal (mean = 38 ml. per liter, S.D. = ± 4, n = 28) or group II (mean = 39 ml. per liter, S.D. = ± 7, n = 10). The difference

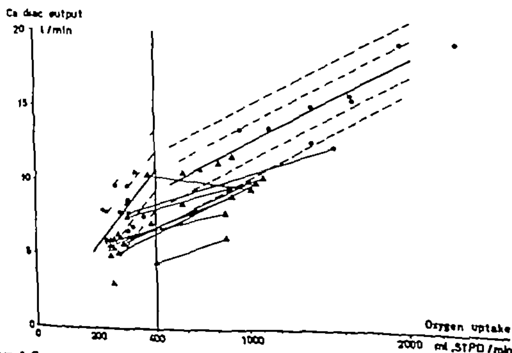


Fig. 2. Correlation between cardiac output and oxygen uptake at rest (left panel) and during exercise (right panel). Regression lines and symbols as in Fig. 1. In cases with abnormally low cardiac output during exercise, the values at rest and during exercise are connected by continuous lines. Normal regression equation: Q = 6.24 + 0.0061 VO_2, r = 0.96, S.E.E. = ±1.31, n = 97.

Table II *The data obtained by cardiac catheterization at rest and during exercise*

Case No	Work load (kpm /min)	Pulse/min.	Oxygen uptake (ml /min)	A V O_2 difference (ml /L.)	Cardiac output (L./min)	Stroke volume (mL.)	Systolic period (1/100 sec)
1	Rest	141	214	27	7 81	55	24 6
2	Rest	86	229	28	7 95	88	28 6
3	Rest	69	206	33	6 20	90	26 4
	250	103	698	65	10 8	104	
	500	141	1084	80	13 5	96	22 0
4	Rest	78	325	47	6 87	88	32 0
	600	142	1518	93	16 38	115	
5	Rest	99	253	32	7 88	79	27 8
	400	149	1227	86	14 32	96	21 2
6	Rest	71	334	32	10 50	143	30 9
	400	114	1091	72	15 17	133	26 7
	800	154	1938	101	19 17	125	
7	Rest	79	290	41	7 10	90	30 7
	600	156	1481	11	13 80	89	
8	Rest	119	191	34	5 60	47	25 1
9	Rest	81	313	36	8 60	106	27 6
	600	143	1650	107	15 50	108	23 9
10	Rest	79	232	32	7 85	100	31 2
	200	123	710	69	10 29	82	
11	Rest	82	273	29	9 60	114	30 0
	300	104	948	70	13 50	130	27 0
	600	131	1391	92	15 10	115	21 8
12	Rest	82	288	37	7 72	94	29 6
	400	135	1133	83	13 62	101	24 6
13	Rest	105	309	32	9 63	92	31 1
	150	144	648	59	11 02	77	
14	Rest	68	312	41	7 68	113	37 1
15	Rest	71	243	43	5 7	80	37 0
	300	105	948	79	12 0	114	
	600	156	1632	103	15 8	101	
16	Rest	81	311	48	6 51	80	31 3
	600	150	1546	125	12 31	82	
17	Rest	57	351	47	7 5	132	34 5
	400	99	1197	95	12 6	126	
	800	138	2207	114	19 3	140	26 0
18	Rest	86	240	41	5 81	68	31 9
	200	132	810	72	11 20	85	26 2
19	Rest	113	208	29	7 80	69	26 1
	200	154	585	56	10 50	68	22 5
20	Rest	84	263	51	5 20	62	33 5
21	Rest	74	308	36	8 50	115	
22	Rest	75	248	42	5 85	79	30 9
	137	97	576	69	8 30	86	29 5
23	Rest	67	252	50	5 00	75	35 9
	400	115	1046	106	9 00	86	30 25
24	Rest	104	406	92	4 40	42	28 9
	200	140	318	137	6 18	44	22 4
25	Rest	89	248	51	4 83	54	

Abbreviations kpm., kilopondmeters, PA, pulmonary arterial PCV pulmonary capillary venous ; LV left ventricular LA, left atrial AV

Pressures (mm Hg)										
PA			PCV	Aorta			LV		LA	AVAI (cm.²/M²)
S	D	M	M	S	D	M	S	ED	M	
27	13	20		117	84	103	134	13	12	1 64
20	10	15		90	60		117	9	9	1 38
31	15	20	15	91	66		117	12		1 46
				125	63					
				123	82	98				
26	11	16	11	107	67	83	120	14		0 85
37	15	24	15	141	83	107				
24	10	17	10	118	73		141	11		0 88
40	14	21		121	79	97				
22	9	16	11	103	70	80	127	12		1 41
28	8	18		114	80	92				
42	9	23		120	88	101				
23	12	17	12	117	73	94	136	15		0 87
16	16	26	14	130	76	100	159	18		
17	13	15		111	79		151	10	10	0 70
26	10	17	11	111	75		203	17	11	0 66
47	16	29		117	75	100	244	22	13	
17	7	13		113	77		182	10	8	0 62
		23		120	78	92	210	15	13	
21	8	14	9	89	69		160	15	10	0 55
30	15	22	15	107	79					
30	17	23	16	116	82	99				
27	13	20	14	135	86	109	185	18	13	0 74
49	18	33		143	89	113	224	21	16	
18	9	14	11	94	64	67	200	16	12	0 59
45	25								20	
31	16	20		103	65	86	197	22	17	0 51
18	8	13	9	114	72	84	164	12		0 61
30	10	19		118	77	91				
44	10	23		130	86	108				
26	16	21	11	136	84	103	178	14	10	0 59
44	30			176	101		212	17	19	
22	15	19	14	94	63		173	18	12	0 60
53	34	45		12	80	100	193	28	25	
56	33	44		120	80	103				
33	11	17		94	68	79	192	14	9	0 39
							245	14	9	
20	6	14		99	70		190	12	10	0 48
34	16			115	79		242	17	13	
33	11	21	18	106	65		175	25	17	0 42
28	14	20		106	72	84	216	26	17	0 47
33	17	26		150	96	117	200	24	17	0 49
41	28	34		158	94	117			19	
26	16	19		118	69	87	172	21	16	0 45
49	24			133	87	107	227	33	27	
80	43	39	43	118	75	93	182	36	35	0 31
110	59	85		163	95	125	252	47		
41	16	31		103	60	75	235	30	20	0 27

...valve area index S systolic D diastolic, M mean ED end-diastolic

Continued on next page.

Table II—Cont d

Case No	Work load (kpm /min)	Pulse/min	Oxygen uptake (ml /min)	A V O_2 difference (ml /L.)	Cardiac output (L./min)	Stroke volume (ml.)	Systolic period (1/100 sec)
26	Rest	77	382	53	7 11	92	37 8
27	Rest	66	280	94	3 0	45	35 5
28	Rest	79	294	52	5 7	72	37 3
	300	129	994	100	10 0	77	26 7
29	Rest	75	252	40	6 2	83	35 2
	200	107	897	77	11 6	108	30 1
30	Rest	83	304	40	7 54	91	
	400	130	1085	107	10 18	78	
31	Rest	82	280	46	6 1	74	33 0
32	Rest	67	267	46	5 86	88	33 0
	400	139	838	111	7 87	55	
33	Rest	73	245	43	5 7	78	33 4
	300	98	885	99	9 0	91	
34	Rest	80	378	37	10 27	128	34 1
	300	112	1005	105	9 57	85	30 0

Abbreviations Kpm., kilopondmeters PA, pulmonary arterial PCV pulmonary capillary venous; LV left ventricular; LA, left atrial; AV

Table III Cardiac index (L./min / M^2)

Group	Normal*			I			II			III		
	Mean	± S D	n	Mean	± S.D	n	Mean	± S.D	n	Mean	± S.D	n
	4 19	0 76	28	4 89	1 06	7	4 55	0 90	10	3 27	1 00	17

Probability	Normal	I	p > 0 1	I II	p > 0 4
		II	p > 0 2	II III	p < 0 01
		III	p < 0 001	I and II III	p < 0 001

*References 7 and 12

between Groups I and II and the normal subjects is not significant

In normal individuals the mean stroke volume (SV) during exercise is about 2 per cent of the total blood volume [7,13] The average stroke volume at rest and during exercise in Group I is 2.3 per cent in Group II 2 2 per cent and in Group III 1 6 per cent of the blood volume. The difference between Group III and the other two groups is significant. Similarly the mean stroke index is significantly decreased in Group III (42 ml per square meter) compared to Groups I and II (60 ml per square meter) During exercise the stroke volume increased in 3 and decreased in 4 patients and it was unchanged in the remaining

In 28 patients the aortic pressure tracings were satisfactory for the measurement of systolic period which is estimated from the beginning of the upstroke to the incisura (Table III) At rest in 10 patients (3 in Group II and 7 in Group III) the systolic period is longer than two standard errors of estimate in relation to heart rate (Fig 3) All in Group I are within the

Pressures (mm. Hg)										AVAI (cm²/M²)
PA			PCV	Aorta			LV		LA	
S	D	M	M	S	D	M	S	ED	M	
56	24	39	29	125	64		230	43		0 32
96	43	62	30	124	58	83	199	32		
47	23	34		106	57	79	263	33	26	0 32
82	48	65		168	84	118	323	43	48	
38	16	26		119	73	92	230	22	12	0 31
58	27	44		132	81	103	252	32	26	
24	13	17	9	112	65	87	230	25		
50	22	35	35	138	75	100				0 37
47	17	29	12	106	59		163	24	13	0 48
28	11	17	15	148	84	99	226	20		0 39
63	40	52	40	185	91	132				0 32
29	10	16	8	118	64	88	220	25	10	
56	19	39		134	79	104	248	33	27	
35	11	23	16	153	82	106	236	21	15	0 49
33	19	34		154	90	116			30	

...ic valve area index; S, systolic; D, diastolic; M, mean; ED, end-diastolic.

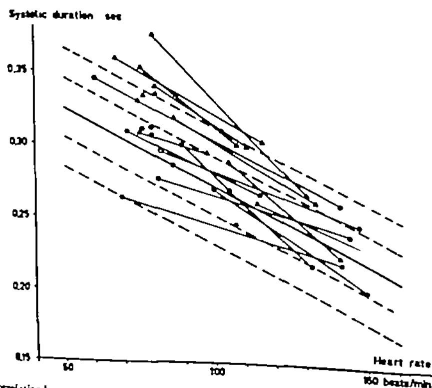


Fig. 3 Correlation between the systolic duration and the heart rate at rest and during exercise. Regression lines and symbols as in Fig. 1. Normal regression equation: systolic duration = 37.8 − 0.106, heart rate S.E.E. = ±2.03, r = 62...

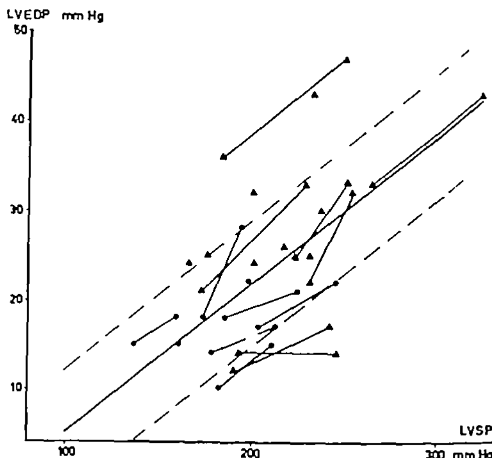


Fig 4 Correlation between the left entricular end-diastolic pressure (*LVEDP*) and the left entricular systolic pressure (*LVSP*) The cont uous l ne ndicates regression and the broken lines one tandard error of estimate. Regression equation LVEDP = 0 145 × LVSP − 6.95 S.E E. = ±7 18 n = 43 The resting and exercise values are connected by cont n o l nes. Symbols a in Fig 1

normal range In 15 the systolic duration was measured during exercise Four of these show abnormally prolonged systolic period at rest while only one is prolonged during exercise

The systolic ejection period is measured from the simultaneous aortic and left ven tricular pressure tracings as the period during which systolic gradient is present across the aortic valve The mean ratio of systolic ejection period over the cardiac cycle in seconds is 37 per cent in Group I 38 per cent in Group II and 40 per cent in Group III at rest The differences are not significant

The mean pulmonary capillary venous (PCV) pressure was 0.8 mm Hg higher than the mean left atrial pressure in 11 patients in whom both pressures were measured at rest. In 24 cases the left atrial pressure was recorded and in the remain ing 10 the PCV mean pressure was used in the following calculation The mean left atrial or PCV pressure is 11 4 mm Hg in Group I 10 7 mm Hg in Group II and 17 7 mm Hg in Group III The difference between Group III and Groups I or II is significant. During exercise the left atrial or PCV mean pressure was measured in 19 cases The pressure increased in all except one In 12 cases the mean left atrial or PCV pressure is 15 mm Hg or higher at rest and all these patients complained of either dyspnea or chest pain during the exercise test except one (No 14)

The mean left ventricular end-diastolic pressure (LVEDP) was 12 mm Hg in Group I 15 mm Hg in Group II and 25 mm Hg in Group III The differ ence between Group III and Groups I and II is highly significant Of 15 cases with LVEDP above 20 mm Hg at rest all except one belong to Group III In these with markedly elevated LVEDP only one (No 14) was able to perform the exercise test without having any

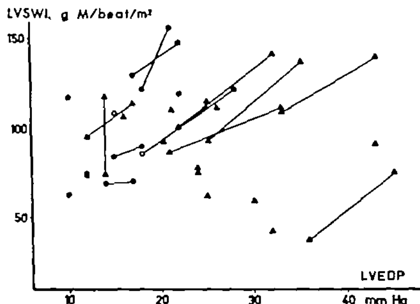


Fig 5 Correlation between the left ventricular stroke work index (*LVSWI*) and the left ventricular end-diastolic pressure (*LVEDP*). The resting and exercise values are connected by continuous lines. Symbols as in Fig. *1*

symptoms and in the remaining 14 either dyspnea or chest pain occurred during the exercise test.

During rest and exercise there is a close positive correlation between the left ventricular systolic pressure and the LVEDP (Fig 4) In every case except one the LVEDP increased during exercise The LVEDP rises more during exercise in Group III than in the other groups.

The resting mean pulmonary artery pressure was above 25 mm Hg in 8 cases of Group III During exercise the mean pulmonary artery pressure increased further in all of these patients (Table II) The mean pulmonary vascular resistance index (unit per square meter) is 1 25 ± 0 64 in normal individuals, in 1 22 ± 0 21 in Group I 1 36 ± 0.88 in Group II and 4 11 ± 4.83 in Group III It is significantly increased in Group III compared to the normal individuals. During exercise the pulmonary vascular resistance either remained unchanged or increased slightly. The systemic vascular resistance at rest is within normal limits in all except one patient (N 22) in comparison to the normal individuals. During exercise the mean aortic pressure and the systemic resistance changed normally in relation to the cardiac output in all cases except 4 in whom these were abnormally high In no case was the systemic resistance abnormally low in relation to cardiac output at rest or during exercise

The left ventricular stroke work varied from 39 to 130 with the mean of 86 gm M./beat/M At rest the average value in Group I is 71 ± 13 in Group II 100 ± 24 and in Group III 82 ± 25 gm M./beat/M The difference between Groups I and II is significant but the differences between Groups I and III or Groups II and III are not significant In many cases of Group III the stroke work is considerably lower compared to the cases of Group I or II in spite of the marked elevation in the left ventricular end-diastolic pressure (Fig 5) The mean left ventricular work in Group I is 6.2 in Group II 8 1 in Group III 6 6 Kg M./min./M and the mean of the total material is 7 0 Kg M./min./M²

Discussion

Cardiac index has been reported to be either decreased[3, 11] or increased[4-] in pa

tients with aortic stenosis Hancock and Fleming[17] found that cardiac output is above normal during investigation using a transthoracic puncture technique and they attributed this to the increased coronary blood flow In the present study no patient was found to have an abnormally increased cardiac output (in relation to the VO_2) at rest or during exercise In patients with mild to moderate aortic stenosis cardiac output was normal whereas it was significantly reduced in patients with severe stenosis Similar observations were made by Wade and Bishop[19] and others[4, 8]

The basal VO_2 is not increased from the predicted value Although the myocardial blood flow and oxygen consumption is increased in these patients it may not be sufficient to increase significantly the over all cardiac output or basal VO_2

In order to analyze the factors which determine cardiac output and stroke volume in aortic stenosis the hydraulic formula by Gorlin and Gorlin[8] may be expressed $SV = sep \times AVA \times 44.5 \times \sqrt{\Delta p}$ where Δp is the mean systolic gradient. It is evident that with a progressively smaller AVA either sep and/or the pressure gradient must increase in order to maintain the normal cardiac output In patients with severe stenosis the systolic period measured from the aortic pressure curves shows a general prolongation as has been found in other studies[20, 22] and the pressure gradient is markedly increased but these compensatory mechanisms appear to be insufficient to maintain a normal cardiac output.

During exercise the systolic period was found to decrease in patients with aortic stenosis as in normal individuals (Fig 3) As the effective valve area is fixed in severely stenotic valve the mean systolic pressure gradient must increase further during exercise to maintain the stroke volume of rest However as the flow is related to the square root of the pressure gradient and the peak systolic pressure that can be generated by the left ventricle is limited a critical stenosis must result in diminished stroke volume Thus the stroke volume in patients with severe stenosis was significantly reduced compared to the normal group as well as in the patients with mild to moderate stenosis.

A close correlation was found between the capacity to perform exercise and the degree of aortic stenosis. Most patients with mild to moderate stenosis were able to perform exercise reaching a pulse rate of above 160 per minute without symptoms. However in the patients with severe stenosis the exercise tolerance was markedly reduced due to symptoms of anginal pain and dyspnea or fatigue. In this group, the exercise had to be stopped due to these symptoms with pulse rate of only 126 per minute

Dyspnea during exercise tests occurred in patients with elevated left atrial pressure In these patients, the left atrial pressure the pulmonary capillary venous pressure and the pulmonary artery systolic pressure increased further during exercise.

Chest pain during exercise tests occurred in patients with severe stenosis and older age In addition to the increased myocardial oxygen consumption due to the aortic stenosis[23, 24] the coexisting coronary artery disease expected to be present in older patients may explain the high incidence of angina symptoms during exercise in these older patients.

The work capacity corresponding to the heart rate of 170 per minute (PWC_{170}) was possible to measure only in patients with mild to moderate stenosis. In the majority of these patients, the PWC_{170} was normal in relation to their total hemoglobin and the heart volume This is in keeping with their normal stroke volume during exercise as the PWC_{170} depends on the oxygen pulse (VO_2 per heart beat) which is the product of stroke volume and the arteriovenous O_2 difference

The ejection fraction (SV/EDV) is an index of myocardial function Therefore it is reasonable to regard the ratio of stroke volume over the heart volume (SV/HV) as a function of myocardial efficiency This index is found to correlate with left ventricular end-diastolic pressure (Fig 6 $r = -0.76$) aortic valve area index (Fig 7 $r = 0.70$) and age ($r = -0.76$) All these correlation coefficients are highly significant The average SV/HV index is 14 per cent (8 to 20 per cent) in Groups I and II

Strok vol. / heart vol.
20 %
15
10
5
0
10 15 20 25 30 35 40 mm Hg
LVEDP

Fig. 6. Correlation between stroke volume in percentage of the heart volume and the left ventricular end-diastolic pressure (*LVEDP*) $\gamma = -0.76$. Symbols as in Fig. *1*

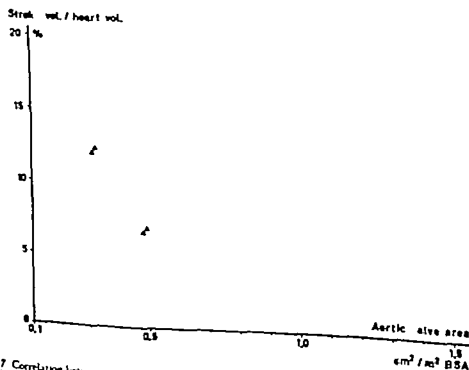


Fig. 7 Correlation between stroke olume in percentage of the heart volume and the aortic valve area. = 0.70. Symbol as in Fig. *1*

and 8 per cent (2 to 12 per cent) in Group III Stroke volume during exercise was used for this calculation except in those who were not exercised during cardiac catheterization

During experimentally increased pressure load on the left ventricle the end diastolic pressure and systolic pressure shows a positive correlation in animals[25] A similar observation was made for human subjects as well[26] A general positive correlation of LVEDP and LV systolic pressure was found in this study at rest and during exercise (Fig 4) During exercise the LVEDP increased in most patients and the rise was more marked in patients with severe stenosis and of older age This increase in LVEDP during exercise signifies the reduced myocardial compliance and the depressed myocardial functions in patients with aortic stenosis. In pulmonary stenosis the positive correlation between the right ventricular systolic and the end-diastolic was also found[27]

In most cases with increased LVEDP the mean left atrial or pulmonary capillary venous pressure remains considerably lower than the LVEDP The importance of the left atrial contraction in left ventricular disease has been pointed out by Braunwald and Frahm[28] They found that the mean left atrial pressure was 0 2 mm Hg lower than the LVEDP in normal individuals but a difference of 9 mm Hg was found in patients with an abnormal left ventricle The difference in these pressures was 1 mm Hg in Group I 4 4 mm Hg in Group II and 7 4 mm Hg in Group III

The average resting left ventricular stroke work was higher (31 per cent) in patients with moderate stenosis than in those with mild stenosis. However in patients with severe stenosis the stroke work was lower (15 per cent) compared to the group of patients with moderate stenosis in spite of the significantly higher LVEDP Thus the left ventricular function is depressed in patients with severe aortic stenosis compared to the milder group

Summary

Hemodynamic studies and estimations of heart volume and work capacity were carried out in 34 patients with pure aortic stenosis and the findings were correlated to the degree of stenosis estimated by the calculated valve area. In a majority of patients with mild stenosis (Group I) and moderate stenosis (Group II) cardiac output stroke volume heart volume, pulmonary vascular resistance, and work capacity were normal However in patients with severe stenosis (Group III) cardiac output and stroke volume were significantly decreased heart volume and pulmonary vascular resistance were increased and the left ventricular function assessed by the LVEDP and stroke work or the coefficient of the stroke volume and heart volume was depressed The exercise tolerance was markedly decreased in Group III due to symptoms of anginal pain or dyspnea In those patients the LVEDP was markedly elevated The LVSP and LVEDP showed a positive correlation at rest and during exercise The LVEDP and LVSP increased during exercise in most patients

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Competitive rhythms with synchronous standby (demand) pacemakers

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Julian Aroesty M D
Boston Mass

Atrioventricular conduction is at least transiently re-established in approximately 30 per cent of patients after long term artificial pacemaker implantation for treatment of complete heart block [1-3] A functioning atrioventricular conduction system permits competition between normal ventricular excitation and that from an implanted pacemaker In this setting a fixed rate pacemaker stimulus may fall on the T wave (vulnerable period)[4] of a normally conducted beat Increased interest in so-called demand pacemakers[5-7] has followed reports of ventricular arrhythmias and sudden death presumably related to pacemaker stimuli fortuitously occurring in the vulnerable period of a competing beat

In one widely employed type of synchronous standby (demand) pacemaker (Ectocor 129 E series Cordis Corporation Miami Fla.) there is a 400 msec refractory period during which time the unit can neither detect nor emit an impulse From 400 msec. to approximately 860 msec after a pacemaker stimulus the unit is in an alert phase able to detect spontaneous ventricular activity and to fire synchronously with a spontaneous beat that occurs during this interval If spontaneous ventricular activity does not occur during the alert interval the pacer will stimulate the heart The refractory period of 400 msec limits the maximum number of synchronized pacemaker responses to approximately 150 beats per minute

It is the purpose of this report to illustrate some limitations of the Cordis synchronous standby (demand) pacemaker in preventing competitive rhythms and in preventing pacemaker stimuli from occurring during the vulnerable period of a competing beat

Case reports

Patient 1 A 60-year-old Caucasian man entered the Beth Israel Hospital with a chief complaint of "light headed" attacks. He had a past history of rheumatic heart disease with mitral stenosis and insufficiency congestive heart failure, paroxysmal supraventricular tachycardia, and cardiac syncope Two years prior to admission the patient developed cardiac syncope which occurred with a mechanism of sinus arrest and he was treated by implantation of a fixed rate epicardial pacemaker which had required two subsequent revisions. The present admission was prompted by intermittent pacemaker failure and on this occasion a permanent transvenous synchronous demand pacemaker was implanted (Ectocor No 129 E 3142) At surgery after the demand unit had been connected and before the epicardial unit had been disconnected, there was a brief period during which both units were effectively competing with each other (Fig 1)

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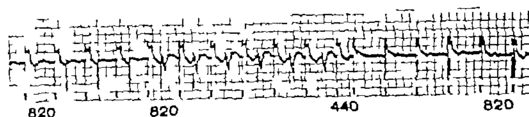


Fig. 1. Competition between the endocardial synchronous demand pacemaker and epicardial fixed-rate pacemaker. Demand pacemaker stimuli are denoted at the bottom of the strip by short vertical lines at 820 msec. intervals (73 beats per minute). The fixed-rate pacemaker stimulus is slightly slower and is seen to follow the demand pacemaker at gradually longer intervals. After the fifth beat the fixed-rate pacemaker no longer falls in the refractory period of the ventricle and is able to excite the heart. There follows a series of ventricular responses to alternate demand and fixed-rate pacemaker stimuli. This is possible because the fixed-rate stimulus is within the synchronized demand pacemaker's refractory period and is not sensed. However, when the fixed-rate stimulus occurs at 440 msec. from the previous demand pacemaker stimulus, the demand pacemaker synchronizes its impulse to that of the fixed-rate stimulus. Thereafter the demand pacemaker again fires at an 820 msec. interval and is again followed by the fixed-rate pacemaker stimulus at gradually longer intervals. The last two beats are fusion beats and have changing configurations. (For purposes of reproduction, pacemaker artifacts were darkened in both figures.)

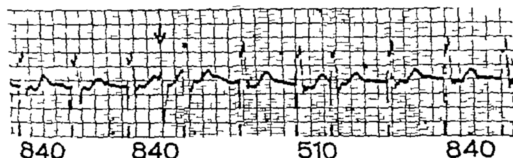


Fig. 2. Pacemaker stimulus falling on the vulnerable period of a competitive beat. The synchronized demand pacemaker is driving the heart with stimuli at 840 msec. intervals (71 beats per minute). The third beat is followed by a ventricular premature beat denoted by the arrow which is within the pacemaker's refractory period. The ventricular beat is not sensed by the pacemaker which fires on the apex of the premature T wave. The pacemaker synchronized at 150 msec. to the R wave of a conducted supraventricular impulse (not obviously supraventricular from this monitor lead) which occurred within the pacemaker's alert period.

Patient 2. A 75-year-old Caucasian woman entered the Beth Israel Hospital with a chief complaint of dizzy spells, of one month's duration. During the four days prior to admission her pulse was documented to be between 40 and 60 beats per minute during symptoms of dizziness. There was a past history of arteriosclerotic heart disease with angina pectoris and electrocardiographic evidence of myocardial infarction. The patient had had hypertension for many years and was treated with hydrochlorothiazide. The admission electrocardiogram revealed an old anteroseptal myocardial infarction, an underlying atrial pacemaker with first degree atrioventricular block, intermittent second degree block, and nodal escape beats. On the fourth hospital day a permanent transvenous synchronous demand pacemaker was implanted (Ectocor No. 129 E-2315). Early after implantation, ventricular premature beats occurred, some of which had a competing pacemaker stimulus inscribed during the vulnerable period of their T wave (Fig. 2).

Discussion

Two varieties of competitive rhythms which can occur with synchronized demand pacemakers are presented. The behavior of the artificial stimulus of a fixed-rate pacemaker has been likened to ventricular parasystole. Therefore, the events illustrated in the example of a fixed-rate pacemaker in competition with a synchronous demand pacemaker could occur spontaneously. When the ventricle is excited during the pacemaker's refractory period the depolarization is not sensed and the

Competitive rhythms with synchronous standby (demand) pacemakers

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In one widely employed type of synchronous standby (demand) pacemaker (Ectocor 129 E series Cordis Corporation Miami Fla) there is a 400 msec refractory period during which time the unit can neither detect nor emit an impulse. From 400 msec. to approximately 860 msec after a pacemaker stimulus the unit is in an alert phase able to detect spontaneous ventricular activity and to fire synchronously with a spontaneous beat that occurs during this interval If spontaneous ventricular activity does not occur during the alert interval the pacer will stimulate the heart. The refractory period of 400 msec limits the maximum number of synchronized pacemaker responses to approximately 150 beats per minute

It is the purpose of this report to illustrate some limitations of the Cordis synchronous standby (demand) pacemaker in preventing competitive rhythms and in preventing pacemaker stimuli from occurring during the vulnerable period of a competing beat

Case reports

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Electrocardiogram, vectorcardiogram and hemodynamics in ventricular septal defect

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Patients with ventricular septal defect (VSD) are usually selected for surgery after estimating shunt size, pulmonary artery pressure, and pulmonary vascular resistance. Although these data can be obtained by cardiac catheterization, indirect methods which can be repeated frequently should be valuable. Experience with electrocardiography and vectorcardiography, however, has not been universally satisfactory, possibly because of the lead systems, the wide range of ages, and the complex hemodynamics. There may be almost any combination of nearly normal right ventricle (RV), pressure or volume overload of the RV (PORV or VORV), normal left ventricle (LV), or one that is volume overloaded (VOLV).

This study was an attempt to find simple measurements of ECG or VCG which would reflect with reasonable accuracy pulmonary pressure, flow, resistance, or related parameters. The promise shown by newer VCG lead systems[4] and availability of computerized techniques for analysis encouraged reappraisal.

Patients and methods

Twenty-five patients with isolated VSD whom cardiac catheterization and recordings of VCG and ECG were made during the same hospitalization were selected. Ages ranged from 3 months to 30 years (Table I). Seventeen were female. None was in heart failure or had complete bundle branch block (BBB) but one (Patient No. 5) had VCG and ECG criteria for incomplete right BBB. Diagnosis was established by right and left heart catheterization and cineangiocardiography.

The VCG lead system of Helm, which employs large sponge electrodes on the chest, was used. The theory, technical details, and normal values have been described elsewhere. Frontal, horizontal, and right sagittal planes (fp, hp, sp) were recorded. P and T loops frequently were deleted electronically to clarify initial forces.

QRS loops were quantitated by measuring five or six vectors identified by morphology. This depends on locating major changes in direction defined as at least 75 degrees in two or more planes. Q, the septal vector, is the first. R is the most leftward point, and S is the first change 12 msec. or more past R. S is a second change 12 msec. or more past S and is inconstant. M is the maximum vector in

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pacemaker will fire at approximately 860 msec after the previous pacemaker discharge (or will fire synchronously with a spontaneous beat occurring within its alert period) It is possible for the pacemaker stimulus to fall on the vulnerable period of any beat of supraventricular or ventricular origin which occurs during the latter part of the pacemaker's refractory period (Fig 2) Ventricular excitation in the pacemaker's refractory period may originate from normally conducted beats, pacemaker induced re-entry beats[10] or ventricular premature beats. The last are particularly prone to occur due to endocardial injury following placement of the pacemaker electrode at the cardiac apex

The possibility of a pacemaker stimulus firing in the vulnerable period of a competitive beat is diminished but not precluded by the choice of a synchronous demand pacemaker It is suggested that ventricular ectopic beats be treated with suppressive agents after implantation of a synchronous demand pacemaker as might be done after implantation of a fixed rate pacemaker

Summary

Two cases are presented which illustrate some limitations of synchronous standby (demand) pacemakers in preventing competitive rhythms. The possibility of a pacemaker stimulus firing in the vulnerable period of a competitive beat is diminished but not precluded by the choice of a synchronous demand pacemaker

The authors wish to thank Drs. Richard Wolff and David Ayman for permission to use the case histories of Patients 1 and 2, respectively Dr Howard Frank implanted the instrument in both cases.

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Horizontal plane			Spatial voltage (mv.)			ECG		Pattern ECG	Diagnosis VCG
s0	∠R	∠S	Q	R	S	Axis	Max Q		
0 3	15	218	0 3	1 6	0 9	70	0 10	R	R
0 1	336	306	0 1	1 7	1 3	35	0 08	N	N
0 2	344	287	0 3	2 4	1 3	40	0 50	L_4	N
0 5	16	305	0 6	3 0	0 4	34	0 60	L	L_4
0 5	28	149	0 5	2 5	0 8	−42	0 50	R_4L	RL
0 6	346	226	0 8	2 9	1 1	57	0 40	R_4L_4	R L
0 1	1	255	0 1	1 6	0 6	− 4	0 05	R L	N
1 1	355	283	1 1	3 9	1 3	70	0 60	L_4	L_4
0 4	41	256	0 4	1 9	1 2	90	0 20	R L	R
0 3	19	225	0 8	2 4	2 6	−36	0 10	L_4	L_4R
0 5	9	190	0 5	3 3	1 2	75	0 40	R L_4	R L
1 8	54	222	1 8	6 3	2 3	57	0 60	R_4L_4	RL
0 7	46	223	0 8	2 2	1 7	67	0 80	P_4L_4	RL
0 5	28	237	0 7	2 5	1 0	102	0 40	R_4L_4	R_4L_4
0 6	334	202	0 6	1 9	1 6	80	0 30	R_4L	R L
2 2	311	—	2 8	2 4	—	100	0 10	R_4L	L_4
0 6	28	194	0 8	3 3	2 4	80	0 55	RL	R L
1 8	47	226	2 0	2 5	2 6	70	1 30	R_4L_4	R L
0 9	7	179	0 9	1 9	1 4	128	0 60	L_4	R L
0 5	45	219	0 5	1 8	0 8	87	0 05	R_4	R L
1 2	40	145	1 2	2 1	1 3	−94	0 30	R L	R L
0 1	74	202	0 4	2 0	1 5	148	0 10	RL	R
0 3	47	259	0 6	2 6	1 4	44	0 15	RL	RL
0 1	43	126	0 1	1 7	1 4	100	0 10	RL	R
0	60	205	0 1	0 6	1 0	250	0 05	R	R

chamber enlargement. Diagnosis of combined hypertrophy was made either when both sets of criteria were present or when advanced evidence of RVH (reverse rotation of the loops occupying more than 42 per cent of the total QRS duration) was accompanied by unexpectedly large left ventricular voltage. When this degree of isolated RVH is present, Q and R tend to be small and were less than one standard deviation above the mean in 93 per cent of 60 patients.[14] Examples using these criteria are shown in Fig 1 and 2.

The following hemodynamic data were recorded systolic pressure in the pulmonary artery (PAP) systemic and pulmonary vascular resistance (SVR, PVR) systemic and pulmonary blood flow (SBF PBF) in liters per minute and per square meter (M²) of body surface area and shunt flow. Ratios of PBF/SBF and PVR/SVR were also calculated. Flow was determined by the Fick principle. For most younger children a basal oxygen consumption of 135 c.c./M²/min was assumed. PVR was estimated in resistance units (PVR = mean PAP minus mean left atrial pressure/PBF/M²). Normal limits in this laboratory are considered to be 2 to 4 units but should be less if flow is increased and vascular response is completely normal.

The data sheet for each patient contained 15 hemodynamic, 40 VCG and 12 ECG measurements. On the assumption that pulmonary pressures, flows, resistances, and age would influence the ECG and VCG most, the data was examined by dividing patients into four overlapping groups I all patients (n = 25) II patients over one year of age but excluding Patient No 5 who had incomplete right BBB (n = 18) III those whose PVR's were less than 2.2

Table I Important data on individual patients

Patient No	Age (yr)	P.A. systemic pressure (mm Hg)	P.A. flow (L/min/M²)	P.V.R. (units)	Time R (msec)	Frontal plane vR	Frontal plane vS/R	Frontal plane ∠M
1	18	19	4 0	0 7	36	1 6	0 49	60
2	29	20	3 5	1 1	44	1 6	0 48	46
3	7	25	16 4	0 3	36	2 3	0 22	36
4	5	26	9 0	0 6	34	2 9	0 11	30
†5	18	28	5 2	1 2	48	2 2	0 33	356
6	4	30	8 2	1 1	36	2 8	0 38	45
7	16	30	10 0	1 0	36	1 6	0 20	24
8	1	32	14 4	0 8	32	3 9	0 09	63
9	9	34	11 6	0 9	31	1 7	0 42	58
10	30	34	11 2	1 0	35	2 2	1 09	246
11	2	35	9 8	1 8	32	3 2	0 35	43
12	1/6	39	30 4	0 4	20	4 4	0 41	43
13	1/3	39	42 0	0 3	20	1 8	0 67	80
14	5	45	7 7	3 5	32	2 3	0 24	37
15	3	46	12 9	0 9	34	1 8	0 81	70
16	1/4	47	17 7	1 3	30	1 6	—	97
17	1/3	59	30 5	1 0	25	3 3	0 84	79
18	1/6	62	15 4	2 1	19	1 6	1 40	92
19	3	70	18 2	1 7	31	1 8	0 76	23
20	6	77	20 0	3 6	24	1 6	0 46	75
21	2	85	16 5	3 2	26	1 8	0 62	66
22	2	86	6 6	9 0	27	1 0	1 47	156
23	17	88	6 5	7 1	24	2 1	0 31	74
24	15	116	5 9	12 2	26	1 2	0 96	36
25	22	127	2 8	22 0	38	0 3	2 90	204

PA, Pulmonary artery P V R pulmonary vascular resistance Angles and axes measured in degrees.
*R, L, and N indicate evidence for right, left, and no ventricular overload. Subscripts refer to criteria numbers in Table II.
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each plane A vector 20 msec from the beginning of QRS was also quantitated Measurements were made only in fp and hp but sp was often necessary for identification of the vectors. The timing position and voltage in each plane and spatial voltage were determined for each A system of notation was used in which characteristics such as time angle and voltage (t, ∠ v) are used as prefixes for the designated vector and the planes (fp hp sp) as subscripts. For example tR refers to the time of the R vector vR_{fp} and $\angle R_f$ to its voltage and position in the fp The subscript 3 refers to the three-dimensional or spatial voltage of a vector (e g vR_3) determined from its projection on X Y and Z coordinates (spatial voltage = $\sqrt{x^2+y^2+z^2}$) [7] The angular reference system devised by Helm[10] was used to record position. All voltage ratios of R/Q and S/R and the angle between S and R in hp ($\angle$S R_{hp}) were noted

From the ECG familiar criteria for detecting pressure or volume loading were measured (Table II) These included mean axis voltage of R R and S in V_1 and their ratios voltage of R and S in I and their ratio voltage of Q waves in limb leads and V_5 and V_6 voltage of R in V_5 and V_6 and the sum R_{V5} or R_{V6} + S_{V1} No quantitation of the T wave was made Values considered normal at different ages were simplified from the tables of Burch[11] A valuable nonquantitative sign of biventricular enlargement was high voltage diphasic midprecordial complexes described by Katz and Wachtel.[12]

VCG criteria for left and right ventricular hypertrophy (Table II) were derived from a comparison of normal values with the changes noted in lesions causing single

Horizontal plan			Spatial voltage (mv.)			ECG		Pattern ECG	Diagnostic VCG
rQ	∠R	∠S	Q	R_s	S	Axis	Max Q		
0.3	15	218	0.3	1.6	0.9	70	0.10	R	R
0.1	336	306	0.1	1.7	1.3	35	0.08	N	N
0.2	344	287	0.3	2.4	1.3	40	0.50	L	N
0.5	16	305	0.6	3.0	0.4	34	0.60	L	L
0.5	28	149	0.5	2.5	0.8	−42	0.50	R L	R L
0.6	346	226	0.8	2.9	1.1	57	0.40	R L	R L
0.1	1	255	0.1	1.6	0.6	−4	0.05	R L	N
1.1	355	283	1.1	3.9	1.3	70	0.60	L	L
0.4	41	256	0.4	1.9	1.2	90	0.20	R L	R
0.3	19	225	0.8	2.4	2.6	−36	0.10	L	L R
0.5	9	190	0.5	3.3	1.2	75	0.40	R L	R L
1.8	54	222	1.8	6.3	2.3	57	0.60	R L	R L
0.7	46	223	0.8	2.2	1.7	67	0.80	R L	R L
0.5	28	237	0.7	2.5	1.0	102	0.40	R L	R L
0.6	334	202	0.6	1.9	1.6	80	0.30	R L	R L
2.2	311	—	2.8	2.4	—	100	0.10	R L	L
0.6	28	194	0.8	3.3	2.4	80	0.55	R L	R L
1.8	47	226	2.0	2.3	2.6	70	1.30	R L	R L
0.9	7	179	0.9	1.9	1.4	128	0.60	L	R L
0.5	45	219	0.5	1.8	0.8	87	0.05	R	R L
1.2	40	145	1.2	2.1	1.3	−94	0.30	R L	R L
0.1	74	202	0.4	2.0	1.5	148	0.10	R L	R
0.5	47	259	0.6	2.6	1.4	44	0.15	R L	R L
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The data sheet for each patient contained 15 hemodynamic, 40 VCG and 12 ECG measurements. On the assumption that pulmonary pressures, flows, resistances and age would influence the ECG and VCG most, the data was examined by dividing patients into four overlapping groups: I, all patients (n = 25); II, patients over one year of age but excluding Patient No. 5 who had incomplete right BBB (n = 18); III, those whose PVR's were less than 2.2

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Patient No	Age (yr)	P.A systemic pressure (mm Hg)	P.A flow (L/min/M²)	P V.R (units)	Time R (msec.)	Frontal plane		
						vR	vS/R	∠M
1	18	19	4 0	0 7	36	1 6	0 49	60
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3	7	25	16 4	0 3	36	2 3	0 22	36
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6	4	30	8 2	1 1	36	2 8	0 38	45
7	16	30	10 0	1 0	36	1 6	0 20	24
8	1	32	14 4	0 8	32	3 9	0 09	63
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15	3	46	12 9	0 9	34	1 8	0 81	70
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17	¼	59	30 5	1 0	25	3 3	0 84	79
18	½	62	15 4	2 1	19	1 6	1 40	92
19	3	70	18 2	1 7	31	1 8	0 76	23
20	6	77	20 0	3 6	24	1 6	0 46	75
21	2	85	16 5	3 2	26	1 8	0 62	66
22	2	86	6 6	9 0	27	1 0	1 47	156
23	17	88	6 5	7 1	24	2 1	0 31	74
24	15	116	5 9	12 2	26	1 2	0 96	36
25	22	127	2 8	22 0	38	0 3	2 90	204

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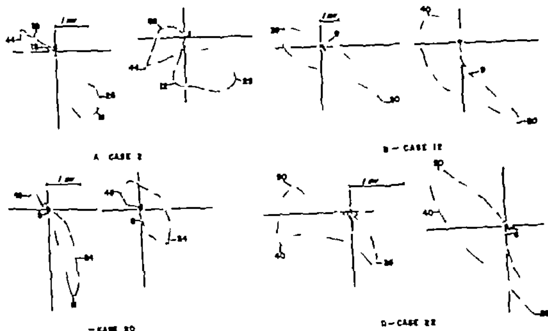


Fig. 2. These four sets of loops ere selected to illustrate patterns of combined hypertrophy and their impl cation. Timing interruptions are every 4 msec. and the sharp ends of the dashes indicate direction. A 1 mv calibration is displayed for each set. Only frontal (left) and horizontal (right) loops are illustrated for each patient but the sagittal plane as frequently used in identifying the vectors. The digits reflect the time (msec.) from the onset of QRS to the Q, R, S, and S' vectors.

A (Case #21). The magnitude of the pulmonary pressure (85 mm. Hg) is suggested by the secondary clock se loop about the S point in the horizontal plane involving 50 per cent of the QRS duration nd by the acute gle (105 degrees) between S and R vectors in the hp. The pulmonary hypertension would be suspected to be principally of the kinetic type (PVR = 3.2 nits). The enormous Q vector (Q = 1.2 mv) and a spatial R voltage above average in the presence of such triking evidence of RVH is considered to reflect additional LVH. An S vector (58 msec.) was lso identified.

B (Case #12). This VCG also suggests combined ventricular enlargement. Left ventricular vectors are enormous (Q_1 = 1.8 mv. R_1 = 6.3 mv). Additional RVH ith high PVR is suspected because of the clockwise horizontal loop with narrow S-R angle (168 degrees). The patient, however was 3-month-old infant with tremendous pulmonary flow but normal pulmonary artery pressure nd resistance. The above criteria for right ventricular hypertrophy are obviously unreliable t this age. The true situation might be suspected because of the discrepancy bet een the exceptional magnitude of left ventricular vectors and pparent evidence of severe pulmonary hypertension. Note also that the Q vector is directed superiorly nd tilted toward the left. This pattern is common even in normal children w th vertical electrical position.

C (Case #20). The presence of pulmonary hypertension (77 mm. Hg) and right ventricular hypertrophy is established by the narrow S-R angle (174 degrees) in the horizontal plane. It is unusual, however for the loop to remain counterclockwise with this relationship bet een S and R. In the presence of RVH the leftward maximum ector (31) of such high voltage (M 2.5 mv) would be interpreted as evidence for additional left entricular hypertrophy. The inferior direction of Q with vertically positioned loop is considered bnormal also but the reasons are not apparent.

D (Case #22). Right ventricular hypertrophy pulmonary artery pressure above 60 mm. Hg, and high resistance are predicted from the clockwise loop and the narrow S-R angle (128 degrees) in the horizontal plane. The R vector (R_1 = 2.0 mv) is larger than average for this age but falls short of present criteria for combined hypertrophy. The same abnormality of Q position (inferior with right mean axis) is present as in C.

was compared. A point was awarded for each entricle correctly assessed. Criteria (Table II) were liberal since the existence of heart disease was already established. When pulmonary artery pressure and re sistance are normal primarily VOLV exists, but some shunting also occurs in diastole (VORV)[14] and the RV may help to expel blood shunted in systole.[14] It was therefore assumed that all patients had biventricular overload except Patient No. 25 who had an Eisenmenger syndrome with no left to-

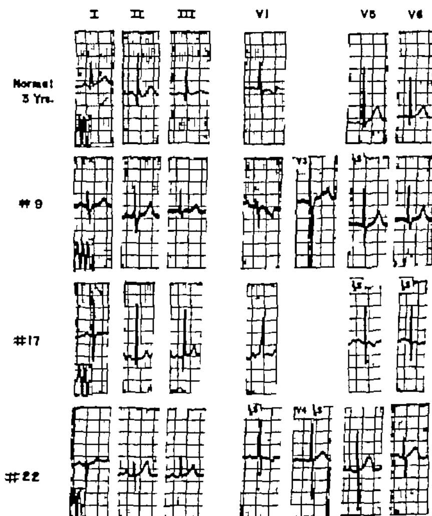


Fig 1 Electrocardiograms (ret uched) illustrating various patterns and their hemodynamic implications A 1 mv signal is recorded for each nder Lead I

Top Traci g from a normal 3-year-old girl. Note deep Q wa es (0 4 mv) VCG is n Fig 2

Case #9 ECG suggests biventricular enlargement. Note the S pattern, large diphasic midprecordial complexes (Katz Wachtel sign) nd large peaked T waves. The pattern of VORV (rr'S complex in V) usually accompanies a pulmonary artery pres ure of less than 45 mm. Hg

Case #17 Biventricular enlargement. Preservation of the deep Q and large left precordial R w ves of left ventricular volume o erload in the presence of right ventricular pressure overload i V This combination usually indicates moderate pulmonary hypertension due to high flow and a relati ely normal pulmonary vascular resistance.

Case #22 Biventricular enlargement Right ventricular enlargement is apparent from the frontal plane axis and the pattern in V The larger d phasic complexes i midprecordial lead suggest add tional left ventricular hypertrophy In contra t to Case 17 however the tiny Q waves uggest that pulmonary vascular resistance is sharply increased

units (n = 18) and IV those whose PAI was less than 40 mm Hg (n = 13) Coefficients of correlation were determined by a standard computer program for the relationship of all 67 variables to each other and repeated for the four groups

Large Q waves or vectors distinctive features of the pattern of VOLV were given special attention[14] Those with abnormally large vectors for their age were compared to the others in respect to pulmonary pressure resistance and flow Those whose Q vectors tilted to the left and who therefore had tiny or absent left sided Q waves in the ECG were treated similarly Finally normal controls matched for age and sex were selected for each patient and statistical comparisons were made of vQ₅ vQ₆ ratio of vR₅ to vQ and for the largest Q wave found in the limb leads V₅ or V₆

The accuracy of ECG VCG and both together in identifying ventricular overload

right shunt. If PAP was less than 40 mm Hg and PVR less than 2.0 units, VORV was considered present (Patients 1 to 13). With higher values, an additional PORV was assumed.

Results

Table I lists important measurements for each patient. There were no useful linear correlations between ECG and hemodynamics, but rough estimates were possible from some patterns. Abnormally large Q waves (>0.4 mv.) were found in 12 cases and although PAP ranged from 19 to 70 mm. Hg 11 had resistances under 2.2 units. The four patients with right axis (>100 degrees) had elevated PAP (45 to 127 mm. Hg) but variable PVR (1.7 to 22.0). Left axis (<0 degrees) found in four patients, was associated with PAP of 25 to 85 mm. Hg and PVR of 1.0 to 3.2. The patterns in V_1 of VORV (RSr' RSR' and Rr'S) and PORV (rRs, Rs R) usually served to separate patients with PAP above and below 45 mm Hg. The ECG pattern of VORV was found in 6 of the 13 patients without PORV and the pattern of PORV only once. In the 12 cases that had additional PORV the typical ECG findings were noted eleven times and that of VORV only once.

The detection rate for biventricular enlargement by ECG VCG and pooled interpretations was, respectively 82 74 and 88 per cent. In cases with only VORV RVH was missed in about half by both

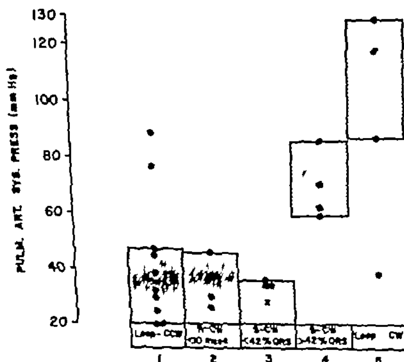


Fig. 4 The rotational features of the loops in the horizontal plane have been related to pulmonary artery systolic pressure. The boxes enclose the useful ranges three exceptions (columns 1 and 5) are visible. Those patients with completely clockwise (CW) loops (column 5) have pressures of 86 to 127 mm. Hg and pulmonary vascular resistances of 9 to 22 units. The exception was 3-month-old infant with an enormous flow (Case 12, Fig. 2) Those with secondary clockwise loops about the S point which encompass more than 42 per cent of the total QRS duration (column 4) also have pulmonary hypertension (59 to 85 mm. Hg) but pulmonary vascular resistances remain approximately normal (1 to 3.3 units). Cases with completely counterclockwise loops or with brief reversals of direction about the R and S points (columns 1 2, and 3) generally have pressures under 50 mm. Hg, and with one exception (3.5 units) pulmonary vascular resistances of less than 2.0 units. Two unexplained exceptions (Cases 20 and 23) occur in column 1. Both have pressures and resistances compatible with those in columns 4 or 5. The pressure range of one (Case 20 Fig. 3) is correctly indicated by the narrowed angle between S and R vectors. The patient with incomplete RBBB is noted (X) in column 3.

Table II Criteria used for identifying ventricular hypertrophy

Left	*Right*	*Combined*
	Electrocardiogram	
1 LAD < 0°	1 r′ in V_1 Voltage of R < 0 7 mv (adults) < 1 4 mv (children)	Mixtures of criteria for RVH, LVH
2 $S_V + R_{V_6}$ > 4 0 mv (adults) or > 5 0 mv (children)	2. R in V_1 > 0.7 mv (adults) > 1 4 mv (children)	5 Katz Wachtel sign
3 R or S > 95% range for age in mid or left precordial leads.	3 Intrinsicoid deflection V > 0.03 sec. (includes rR)	6 Evidence for RVH present and voltage indices for LVH (Q or R) increased
4 2 or 3 positive or borderline but Q > 0 4 mv in limb leads or V_5, V_6.	4 R/S ratio > 1 0 above age 3 > 2 0 age 1–3 > 3 0 age < 1 year	
	Vectorcardiogram	
1 M leftward M > 2 6 mv	1 Voltage S_f > 0.8 mv or ratio (vS/R_f > 0.33 with S clockwise	5 Mixture of criteria for RVH, LVH
2 P or leftward M exceeding 2.2 mv (mean +1 S D) plus at least one of the following a Q > 0 6 mv (adult) or 0 9 mv (children) b Angle M_f < 20° (adults) < 30° (children) c. Angle R_h < 335° d Angle R S_h < 64	2 Position S_h < 2.5 (adults) < 200° (children)	6 Advanced evidence for RVH (S_h clockwise > 42% tQRS) plus at least one of the following a. vR_1 > 2.2 adults, 2.3 children (mean + 1 SD) b. vQ_5 > .35 adults, .60 children (mean + 1 S.D)
	3 S-R $Angle_h$ < 225°	
	4 S clockwise > 42% tQRS	

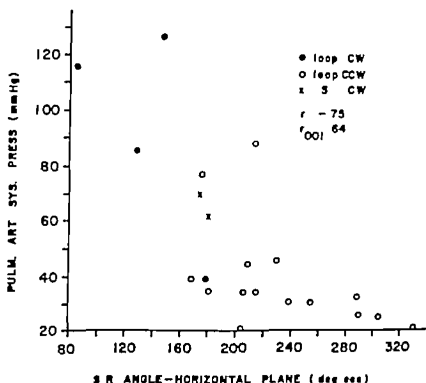


Fig 3 Relation of pulmonary arterial pressure to < S R $_h$. The measurement from VCG or ECG which correlated best with systolic pressure in the pulmonary artery was the wide angle between S and R vectors in the horizontal plane. Normally this is 260 degrees ± 18 in children and young adults. These vectors tend to approach each other anteriorly with increasing pressure loads. The principle direction of rotation for each loop (as in columns 3 4 and 5 Fig 4) is indicated in the legend. Two cases are omitted No 5 thought to have incomplete RBBB and No. 16, in whom no S vector was present. The regression equation is PAP = 127 7 − .37 (∠S R_{hp}) and the standard error of the estimate is 21 mm. Hg

"free wall" vectors (equal R₁/Q ratios) Indeed the size of Q and R are closely related when PAP is normal (Figs. 7 and 8) Large Q vectors were also found however after PORV had developed (Patients 16, 18 19 21 and 23 Fig 2) Patients with large Q vectors did not constitute a homogenous group hemodynamically (PAP 32 to 88 mm Hg PBF 6.5 to 30.4 L./M.² and PVR, 0.4 to 7.1 units)

Six loops exhibited leftward Q vectors. Four (Patients 12 13 15 and 18 Fig 2) seemed to be positional as often seen in normal children The loop was vertical rotation clockwise and Q was superior and tilted slightly to the left. Two however (Patients 7 and 10) probably had abnormal septal activation Both were older the ECGs showed left axis deviation loops were horizontal and rotation was counterclockwise

Discussion

Electrocardiogram Previous reports indicate no linear correlations between ECG measurements and hemodynamics but certain conclusions may be summarized[13] (1) a normal ECG indicates a small defect

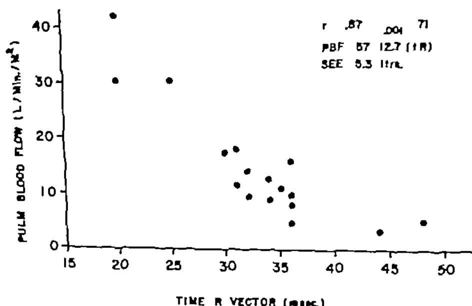


Fig 6 The time of the R vector correlates inversely with pulmonary blood flow index, but only when the pulmonary vascular resistance is normal (< 2.0 units). Since age correlates both with tR (= 0.68) and PBF (r = −0.38) in this group, a multiple regression analysis was performed to see if age had significant influence on the above relation It was found that it did not (variance ratio, 5/659 not significant).

With PVR < 2.1 (= 18)			With PAP < 40 mm Hg (= 13)		
Patients	Control	t(p <)	Patient	Control	t(p <)
72 ± 59	36 ± 24	2 72 (0 02)	53 ± 42	31 ± 21	1 87 (NS)
84 ± 70	41 ± 23	2 87 (0 02)	62 ± 46	37 ± 21	2 24 (0 05)
5 1 ± 4 2	6 2 ± 5 0	−0 89 (NS)	6 3 ± 4 4	7 2 ± 5 6	−0 85 (NS)
43 ± 31	23 ± 12	2 40 (0 05)	38 ± 25	18 ± 09	2 68 (0 05)

but when PORV was also present RVH was nearly always detected (Table II) Examples are illustrated in Figs. 1 and 2

Correlations with numerous VCG measurements were significant ($p < 0.05$) but only the most useful will be mentioned The best gauge of PAP was the wide angle between S and R vectors in HP (Fig 3) Clockwise rotation frequently results and also reflects pressure and resistance levels (Fig 4) Some improvement in prediction of PAP occurs if its relation to $\angle S\ R_{hp}$ and vS/R_{fp} is combined in a multiple regression equation (Fig 5) Pulmonary flow was inversely related to the time of the R vector in patients with low PVR (Fig 6) but poorly for all patients since PORV independently shortens tR [4]

Several comparisons of the initial forces of patients and of controls were made (Table III) Initial vectors are significantly larger in patients but only if infants under one year of age are included Although some values are abnormal in older individuals wide overlapping occurs. Septal vectors did not grow disproportionately to

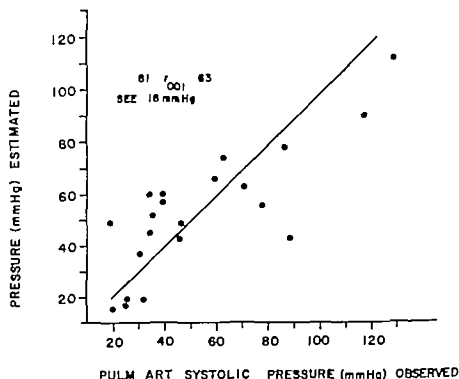


Fig 5 Ventricular septal defect. Comparisons of observed and estimated pulmonary rtery systolic pressures (PAP) The latter were obtained from the voltage ratio of S and R vectors in the frontal plane (vS/R_{fp}) nd the angle between S and R the horizo tal ($\angle S\ R$) The m ltiple regressio equation is PAP = 91 + 0 20 (vS/R_f) − 0.27 ($\angle S\ R_h$)

Table III *Comparison of voltage of initial forces of patients with VSD and age matched controls*

Vector	All patients (n = 25)			Over 1 year of age (= 19)		
	Patients	Control	t(p<)	Patients	Control	t(p<)
vQ_{hp}	64 ± 56	36 ± 21	2 58 (0 02)	45 ± 34	37 ± 18	1 01 (NS)
vQ_{b}	75 ± 64	41 ± 21	2 92 (0 01)	53 ± 33	41 ± 20	1 69 (NS)
vR_{s}/Q	5 3 ± 4 2	6 0 ± 4 4	−0 63 (NS)	6 1 ± 4 4	6 1 ± 4 4	0 03 (NS)
Q_{dur}	36 ± 30	23 ± 11	1 96 (NS)	7 ± 20	22 ± 10	99 (NS)

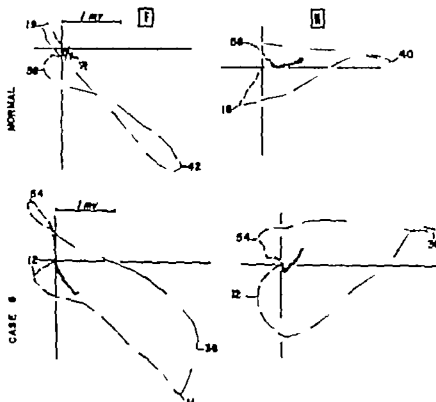


Fig. 8 Frontal (F) and horizontal (H) loops only are displayed. VCG selected from two children to illustrate similarities between normal loops and moderate volume overload of the left ventricle. Details of presentation are the same as in Fig 2

The top set is from normal 3-year-old girl and emphasizes that large Q vectors are not rare when the loop itself is of high voltage. Spatial Q and R vectors are 0.8 and 2.77 mv respectively the direction of T is normal, and volume overload of the left ventricle is suggested (see ECG Fig 1)

The bottom set (Case #6) is also characteristic of the pattern of volume overload of the left ventricle. Spatial Q and R voltages are however very similar to the above normal (0.8 and 2.9 mv respectively). A meaningless (7 msec) reversal of transcription at the R point is also illustrated. Additional mild right ventricular involvement is suggested by the voltage of S in the frontal plane (1 1 mv criterion 1 Table II)

tion to delayed intrinsicoid deflection) is ordinarily a sign of left ventricular hypertrophy particularly VOLV.[n] A physiologic explanation is not apparent. Multivariant analyses indicated that age, QRS duration and voltage played no part.

With pure VOLV Q and R forces tend to increase concomitantly the loop enlarges symmetrically and therefore retains its normal shape. Spatial Q voltage is partly a function of age and values over .8 mv were found exclusively in patients under three years. If infants are excluded Q differs statistically from normal only in greater variability. Although some values are high overlap with normal is so great that separation is statistically unconvincing (Table 3 Fig 8)

With PORV diminution and leftward shift of Q occur probably as a result of increased right septal mass.[n] In VSD however the distortion is frequently incomplete and evidence for VOLV remains (Table II Fig 2). A deep Q wave in the ECG however is more reliable than a large spatial Q vector for predicting a normal PVR presumably because it reflects both increased voltage and normal position for the Q vector

Conclusions

1 The VCG s, the ECG s, and data from cardiac catheterization of 25 patients with isolated VSD were analyzed. A wide range of ages and hemodynamics were represented.

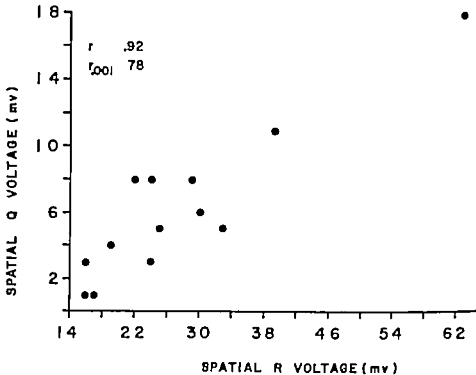


Fig 7 The large Q vectors described in pure volume overload of the left ventricle reflect the increased size of the loop since spatial voltage of Q and R vectors are closely related The relationship breaks down when cases with high pressures are added for Q- and R vector voltages then behave independently

(2) the pure pattern of VOLV reflects a moderate shunt without increased PVR (3) the pure pattern of PORV means that pulmonary and systemic pressures are equal a right to-left shunt exists and pulmonary flow is decreased (4) patients with combined hypertrophy include a wide spectrum of pressures flows and resistances (5) mean QRS axis greater than 120 degrees indicates increased PVR but the left axis has no hemodynamic significance (6) measurements of the T wave add nothing to the analysis of the ECG in VSD [19,20]

Similarly no quantitative relationships were found in this study but certain associations emerged In the presence of large Q waves (>0 4 mv) PVR was rarely increased even if the pattern of PORV was present (Fig 1) The latter may reflect only kinetic pulmonary hypertension but PAP usually exceeds 45 mm Hg [19,20] In those thought to have only VORV the classical ECG was present in about half (Fig 2) The electrical axis was virtually worthless.

The ECG and VCG scored about equally in identifying combined hypertrophy A slight improvement occurs when the interpretations are pooled The ECG patterns of VORV or PORV and the VCG patterns of loop rotation in the horizontal plane have about equal reliability in suggesting pressures and resistance levels.

Vectorcardiogram The best predictor of PAP was the ∠S R_{hp} a measurement which incorporates the anterior shifts of both R and S which occur with PORV The only significant improvement attained with multiple regression equations was by the addition of the ratio of voltages of S and R in the frontal plane (Fig 5) This reflects both the shrinkage of the R voltage and a larger projection of S on the fp as it swings anteriorly [4]

The complete clockwise loop seems to identify those with pulmonary hypertension due to high resistance while reversal confined to approximately the terminal half generally represents moderate pulmonary hypertension due mainly to high flow (Fig 2) In infants however a large shunt may delay disappearance of the normal right ventricular predominance (Figs. 2 and 4)

The inverse relationship between the time of R and flow in patients with low PVR was surprising since a late

Coronary and hemodynamic effects of myocardio-selective beta-receptor blockade by ICI 50172* in the closed-chest dog

Differentiation of coronary and myocardial beta receptors

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Beta-blocking agents are known to diminish myocardial contractility and to reduce coronary flow.[1-4] For the treatment of angina pectoris it would be of great interest to have a drug at disposal that not only blocks sympathetic discharge to the heart but also enhances coronary flow. In this paper evidence will be presented that ICI 50172 possesses these two properties: it blocks myocardial beta receptors and augments coronary sinus outflow. The twofold site of action of ICI 50172, the myocardium on one hand and the coronary vasculature on the other, raises the question whether there are different beta receptors within the myocardium and in the coronary vascular tree.

Methods

Experiments were carried out in 8 male mongrel dogs ranging between 18.5 and 29 kilograms (average 22.8 kilograms). After premedication with 1 to 2 mg of morphine sulfate per kilogram of body weight (BW), the animals were anesthetized with 90 mg per kilogram of alpha chloralose. Heparin was given in a dose of 300 I.E. per kilogram. The animals were intubated with a cuffed endotracheal tube and ventilated with air by means of an Engström respirator. Care was taken to maintain stable normal body temperature throughout the experiment.

Catheters were positioned under fluoroscopic control in the following manner. A Telco† intracardiac pressure transducer was placed in the left ventricle by the transseptal route via the right jugular vein. Through the left carotid artery a No 8 Fr NIH catheter‡ with six laterally opposed sideholes was introduced into the left ventricle. A No 3½ Fr catheter with a thermistor head§ on its tip was located

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§Philips NTC E 205 CE/1K5.

2 The association between several ECG and hemodynamic patterns was noted Q waves greater than 0 4 mv usually meant that pulmonary vascular resistance was nearly normal even if the pattern of pressure loading of the right ventricle was present The latter indicates pulmonary hypertension but does not differentiate between increased flow and resistance The pattern of volume overload suggests pressures below 45 mm Hg

3 The VCG displayed no advantage over the ECG in identifying biventricular disease Both efficiently detected pulmonary hypertension

4 Several VCG measurements however were quantitatively related to hemodynamics. A regression equation utilizing the angle between S and R vectors in the horizontal plane and their voltage ratio in the frontal plane predicts pressure reasonably well Patients with completely clockwise loops in the horizontal plane had pressures above 85 mm Hg and very high resistances but significant terminal reversal was associated with principally kinetic pulmonary hypertension

5 Initial forces Q waves or Q vectors were not statistically significantly larger than in normal controls unless infants under a year of age were included but were consistently more variable The voltage of Q reflects age pulmonary vascular resistance volume overload of the left ventricle and over all loop size

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Experimental and laboratory reports

Coronary and hemodynamic effects of myocardio-selective beta receptor blockade by ICI 50172* in the closed-chest dog

Differentiation of coronary and myocardial beta receptors

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Beta-blocking agents are known to diminish myocardial contractility[1-4] and to reduce coronary flow.[4] For the treatment of angina pectoris it would be of great interest to have a drug at disposal that not only blocks sympathetic discharge to the heart but also enhances coronary flow. In this paper evidence will be presented that ICI 50172[7] possesses these two properties: it blocks myocardial beta receptors and augments coronary sinus outflow. The twofold site of action of ICI 50172, the myocardium, on one hand, and the coronary vasculature, on the other, raises the question whether there are different beta receptors within the myocardium and in the coronary vascular tree.

Methods

Experiments were carried out in 8 male mongrel dogs ranging between 18.5 and 29 kilograms (average 22.8 kilograms). After premedication with 1 to 2 mg. of morphine sulfate per kilogram of body weight (BW), the animals were anesthetized with 90 mg. per kilogram of alpha chloralose. Heparin was given in a dose of 300 I.E. per kilogram. The animals were intubated with a cuffed endotracheal tube and ventilated with air by means of an Engström respirator. Care was taken to maintain stable normal body temperature throughout the experiment.

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via the right thyroid artery in the ascending aorta 1 to 2 cm above the aortic valves. A No 8 Fr NIH catheter with four side holes was placed in the aortic arch through the left femoral artery In 6 of the 8 dogs a No 6 Fr bipolar electrode catheter was advanced through the right femoral vein to the upper part of the right atrium

The aortic pressure was recorded by means of an external Statham transducer Model P23Gb The left ventricular pressure was measured by the Telco tip-manometer from the high fidelity pressure tracings the first derivative (dp/dt) was obtained by a RC differentiator with a time constant of 0 5 msec All recordings were made with a photographic recorder (Model DR/8 Electronics for Medicine)

Cardiac output (CO) was determined from indicator dilution curves following injection of indocyanine green (Cardio Green) into the inferior vena cava with arterial sampling through a Waters† cuvette densitometer During each experimental run four to eight thermodilution curves* were recorded following injection of 5 ml. of ice-cold isotonic saline into the left ventricle through the No 8 Fr NIH catheter

Coronary sinus blood flow was recorded electromagnetically by introducing a catheter with a flow probe on its tip through the left jugular vein into the coronary sinus.[10] The flow probe was connected to a Medicon sine wave flowmeter (Model K 2000) Zero flow determination was obtained in the coronary sinus at the end of each experiment after induction of ventricular fibrillation The flow probe was calibrated in a model experiment by passing isotonic saline (37° C) at constant flow in values varying between 10 to 200 ml per minute

Coronary venous blood was sampled through a special tubing ending in the lumen of the flow probe Coronary venous and arterial oxygen partial tensions (PO_2cv PO_2art) were determined polarographically by the technique of Gleichmann and Lübbers.[11] The pH of the blood samples was measured with a Methrom‡ pH meter

*United States Catheter & Instrument Corp., Glen Falls, N Y
†Model XC 250A, The Waters Company Rochester Minn.
‡Type E 388, Methrom AG, Herisau, Switzerland.

Analysis of data and calculations

Left ventricular contractility was evaluated by the following parameters (1) max dp/dt = maximal rate of left ventricular pressure rise (2) the quotient $\frac{\text{max dp/dt}}{\text{IP}}$—termed contractility index—where *IP* is the instantaneous developed pressure at the point of max. dp/dt[12] (3) the time from the beginning of contraction to max dp/dt (t–dp/dt)[13]

Left ventricular end-diastolic volume (*EDV*) in milliliters was estimated from the following equation[14]

$$EDV = \frac{SV}{1 - K}$$

where SV = stroke volume obtained from the indocyanine green dilution curves, and K = average ratio of the temperature difference from the baseline of aortic blood on successive beats calculated from multiple thermodilution curves. End systolic volume (ESV) = $EDV - SV$ The volumes were normalized on the basis of 10 kilograms of body weight (CI SVI EDVI I = index)

According to Rayford and associates,[8] Hirche and Lochner[16] and Hood[17] practically all the blood of the left ventricular myocardium passes through the coronary sinus Only 1 to 3 per cent of the coronary sinus blood flow (CSBF) is drained from the right ventricle In our experiments this contribution was neglected At the end of the experiment the heart was removed and the weight of the left ventricle plus the septum was determined The CSBF (in milliliters per minute and per 100 Gm) was calculated from the CSBF in milliliters per minute divided by left ventricular weight Myocardial oxygen consumption (MVO_2) in milliliters per minute and per 100 Gm of left ventricular weight was estimated as the product of the coronary arteriovenous oxygen content difference (A V O_2) in volume per cent and coronary blood flow per 100 Gm The A V O_2 was estimated from the A V oxygen saturation difference and the actual hemoglobin and hematocrit The oxygen saturation for each PO_2 value was obtained from the oxygen dissociation curve for canine blood[18]

Left ventricular pressure-time per minute (PTM) in millimeters of Hg times seconds per minute was taken as the product of mean left ventricular pressure during the ejection period (LVSP) the systolic ejection time (ET) and the heart rate (HR) The product of PTM ESV in $\frac{\text{dynes sec.}}{\text{cm. min.}}$ was used to represent tensile stress.[19]

The coronary vascular resistance (CVR) in arbitrary units was calculated as the ratio of mean aortic pressure (MAP) in millimeters of Hg divided by CSBF in milliliters per minute. The systemic vascular resistance (SVR) was estimated in arbitrary units as the ratio of MAP in millimeters of Hg divided by the cardiac output in liters per minute.

Outline of experiments

The following experimental protocol was observed in the 8 dogs. Control values were first obtained then isoproterenol was infused in a dose of 0 034 μg per minute per kilogram and after 5 minutes of administration the hemodynamics were assessed again. After an interval of 30 minutes, ICI 50172* in a dosis of 2 mg per kilogram of BW was injected intravenously over 2 minutes. Seven minutes after completion of th injection an experimental run was carried out Then a second dose of ICI 50172 2 mg per kilogram of BW was njected and after an adaptation phase of 7 minutes the hemodynamics were recorded again At this total dose of 4 mg per kilogram of BW isoproterenol was infused in the same dosage as following the initial control values. An interval of 20 minutes was then permitted Thereafter 4 mg per kilogram of BW of ICI 50172 were i jected the total dosage amounting then to 8 mg per kilogram of BW Seven minutes later the last experimental run was performed.

Additionally three pacing runs were obtained in 6 of the 8 dogs, one at the control state one after a total dose of 4 mg per kilogram and one after 8 mg per kilogram.

*Kindly supplied by Ed. Geistlich AG, Wolhusen, Switzerland

Results

1 Hemodynamic and coronary effects of ICI 50172 2 mg per kilogram After intravenous injection of 2 mg per kilogram cardiac index heart rate, stroke volume index end-diastolic volume index, and ejection fraction remained essentially unchanged The mean systolic left ventricular pressure, the end-diastolic pressure and the mean aortic pressure did not vary either when compared to the control values (Table I Figs. 1 through 4) There were however some indications that left ventricular contractility decreased slightly The contractility index $\frac{\text{max. dp/dt}}{\text{IP}}$ decreased the fall being significant ($p < 0.02$)

Coronary sinus blood flow increased significantly from 60 to 71 mL per minute ($p < 0.05$ see Fig 5) and there was a significant reduction of the coronary vascular resistance ($p < 0.05$) The coronary venous oxygen tension the AV O_2 and the left ventricular oxygen consumption showed only minor and insignificant variations (Fig 5) The tension parameters PTM and PTM ESV which are related to the MVO remained practically unchanged

2 Hemodynamic and coronary effects of ICI 50172 4 mg per kilogram The parameters determined in sinus rhythm are listed in Table I and plotted in Figs. 3 to 5 Those obtained during right atrial pacing are listed in Table II When compared to the control state the cardiac index showed a slight decrease in both runs. The end diastolic volume index increased significantly ($p < 0.05$) under pacing but did not vary in sinus rhythm The ejection fraction decl ned in both instances but the decrease was only significant at a constant heart rate ($p < 0.05$) All pressures tended to rise the augmentation of the left ventricular end-diastolic pressure was significant at the 5 per cent level in spontaneous and paced heart rhythm With respect to the dose of 2 mg per kilogram there was a definite decrease of left ventricular contractil ty indicated by a significant decl ne of max. dp/dt and $\frac{\text{max. dp/dt}}{\text{IP}}$

Table I Hemodynamic and metabolic changes following ICI 50172 at spontaneous heart rate

Dose	CI	HR	SVI	EDVI	EF	LVSP	LVEDP	MAP	SAP	DAP	ET	max. dp/dt
Control	1450 ±150	104 ± 8	14.6 ±1.5	38.5 ±3.3	38.0 ±3.0	136 ± 5	7.9 ±1.2	123 ± 5	143 ± 5	103 ± 6	0.177 ±0.009	31[illegible] ±2[illegible]
ICI 50172 2 mg./Kg p	1406 ±119 NS	103 ± 4 NS	14.0 ±1.4 NS	38.4 ±3.1 NS	36.7 ±2.9 NS	139 ± 7 NS	8.3 ±1.1 NS	128 ± 6 NS	147 ± 7 NS	110 ± 6 NS	0.178 ±0.007 NS	[illegible] [illegible] NS
ICI 50172 4 mg./Kg p	1202 ± 68 <0.05	97 ± 9 NS	13.2 ±1.4 NS	38.1 ±3.1 NS	35.0 ±2.5 NS	141 ± 7 NS	9.6 ±1.3 <0.05	128 ± 6 NS	152 ± 7 NS	110 ± 6 NS	0.185 ±0.008 NS	27[illegible] 2[illegible] <0[illegible]
ICI 50172 8 mg./Kg p	1139 ± 75 <0.01	93 ±11 NS	13.2 ±1.4 NS	40.0 ±4.0 NS	33.3 ±2.0 <0.05	144 ± 6 NS	10.7 ±1.2 <0.05	128 ± 6 NS	149 ± 6 NS	111 ± 5 NS	0.180 ±0.007 NS	2[illegible] ±[illegible] <0[illegible]

CI = Cardiac index (ml./min. 10 Kg. BW) *HR* = heart rate (min.$^{-1}$) *SVI* = stroke volume index (ml./10 Kg. BW); EDVI = left ventri[illegible]
the ejection period (mm. Hg) LVEDP = left ventricular end-diastolic pressure (mm. Hg) MAP = mean aortic pressure (mm. Hg) S[illegible]
rate of left ventricular pressure rise (mm Hg/sec.); $\frac{\text{max. dp/dt}}{\text{IP}}$ = contractility index (sec.$^{-1}$) t-dp/dt = time from the beginni[illegible]
PO_2cv = coronary venous oxygen tension (mm Hg) pH = coronary venous pH; A V O_2 = arteriovenous oxygen content difference (vol[illegible]
Hg sec./min.) PTM ESV = PTM end-systolic volume $\left(\frac{10^4 \text{ dynes sec.}}{\text{cm} \quad \text{min.}}\right)$ CVR = coronary vascular resistance (arb. [illegible]

Body weight 22.8 ± 1.3 Kg., left ventricular weight 97 ± 6 Gm. Mean values ± 1 S.E. of 8 dogs.
P values are referred the control run.
Statistical significance was accepted when p ≤ 0.05
P values < 0.10 (borderline significance) are listed for completeness.

Table II Hemodynamic and metabolic changes following ICI 50172 at constant heart rate

Dose	CI	HR	SVI	EDVI	EF	LVSP	LVEDP	MAP	SAP	DAP	ET	max. dp/dt
Control	1422 ±158	122 ± 6	11.9 ±1.4	36.3 ±3.5	32.7 ±2.8	137 ± 4	5.9 ±1.6	124 ± 5	142 ± 5	107 ± 5	0.166 ±0.013	3026 ±136
ICI 50172 4 mg./Kg p	1275 ±104 NS	122 ± 6 NS	10.6 ±1.0 NS	41.1 ±4.1 <0.05	26.7 ±3.1 <0.05	142 ± 8 NS	7.7 ±1.2 0.05	132 ± 7 NS	149 ± 8 NS	113 ± 7 NS	0.163 ±0.009 NS	2199 ±223 <0.05
ICI 50172 8 mg./Kg p	1318 ±159 <0.10	122 ± 6 NS	10.9 ±1.2 <0.10	42.7 ±6.4 NS	26.4 ±2.5 <0.01	144 ± 8 NS	9.2 ±0.9 <0.05	134 ± 8 NS	154 ± 8 NS	117 ± 6 NS	0.168 ±0.005 NS	2315 ±204 <0.05

Abbreviations see Table I.
Body weight 24.4 ± 1.6 Kg., left ventricular weight 107 ± 6 Gm.
Mean values ± 1 S.E. of 6 dogs.
P values are referred to the control run.

$\frac{dp/dt}{P}$	-dp/dt	CSBF	CSBF/ 100 Gm.	PO_{2cv}	pH	A-V O	M V̇O	PTM	PTM/ ESV	CVR	SVR
32 36	45.3 ±3.0	59.9 ±7.5	64.0 ±8.0	17.6 ±1.3	7.309 ±0.023	12.7 ±0.9	7.8 ±0.9	2539 ±209	1.94 ±0.40	2.23 ±0.22	38.9 ±2.8
14 34 0.02	46.7 ±3.2 <0.10	71.3 ±7.1 <0.05	77.7 ±9.8 <0.05	18.8 ±1.1 NS	7.279 ±0.026 NS	12.4 ±0.9 NS	9.2 ±0.8 NS	2619 ±228 NS	2.02 ±0.39 NS	1.88 ±0.13 <0.05	42.7 ±4.4 NS
.89 3.1 0.02	49.7 ±3.3 <0.01	68.4 ±7.3 0.05	73.1 ±7.9 <0.05	20.6 ±1.2 <0.05	7.323 ±0.016 NS	11.3 ±0.7 <0.05	8.2 ±0.8 NS	2533 ±239 NS	1.73 ±0.25 NS	1.95 ±0.12 NS	48.0 ±4.3 <0.05
37.3 2.6 0.01	50.4 ±2.7 <0.01	70.3 ±10.2 <0.10	75.4 ±11.3 <0.10	22.0 ±1.1 <0.01	7.327 ±0.022 NS	10.7 ±0.6 <0.02	7.8 ±1.0 NS	2418 ±272 NS	1.95 ±0.30 NS	2.00 ±0.20 <0.10	52.6 ±3.9 <0.01

diastolic volume index (ml./70 Kg. BW) EF left ventricular ejection fraction (%) LVEP mean left ventricular pressure during the aortic pressure (mm. Hg) DAP diastolic aortic pressure (mm. Hg) ET systolic ejection time (sec.) max d dt maximal

action to max. dp/dt. CSBF coronary sinus blood flow (ml./min.) CSBF/100 Gm. CSBF per 100 Gm. left ventricular weight

myocardial oxygen consumption (ml./min. 100 Gm. left ventricular weight) PTM left ventricular pressure time per min. (mm

venous vascular resistance (arb. units)

$\frac{dp/dt}{IP}$	-dp/dt	CSBF	CSBF/ 100 Gm.	PO_{2cv}	pH	A-V O	M V̇O	PTM	PTM/ ESV	CVR	SVR
41.6 3.3	46.8 ±1.9	64.0 ±7.1	61.6 ±8.3	17.8 ±1.9	7.313 ±0.012	13.5 ±1.1	8.1 ±1.0	2746 ±222	2.30 ±0.49	2.03 ±0.19	38.0 ±3.8
34.8 ±3.2 <0.05	53.0 ±4.5 <0.10	77.8 ±7.7 <0.05	73.7 ±7.1 <0.05	21.4 ±1.2 <0.10	7.286 ±0.023 NS	12.0 ±0.9 <0.10	8.7 ±0.8 NS	2823 ±245 NS	2.87 ±0.51 <0.02	1.73 ±0.12 NS	44.1 ±3.9 NS
31.9 ±3.1 <0.01	56.2 ±3.7 <0.01	81.6 ±10.3 <0.05	77.0 ±9.9 <0.05	23.4 ±2.0 <0.01	7.312 ±0.036 NS	10.7 ±1.0 <0.02	8.1 ±1.1 NS	2946 ±252 <0.05	3.14 ±0.71 <0.10	1.74 ±0.15 <0.10	44.7 ±4.2 0.10

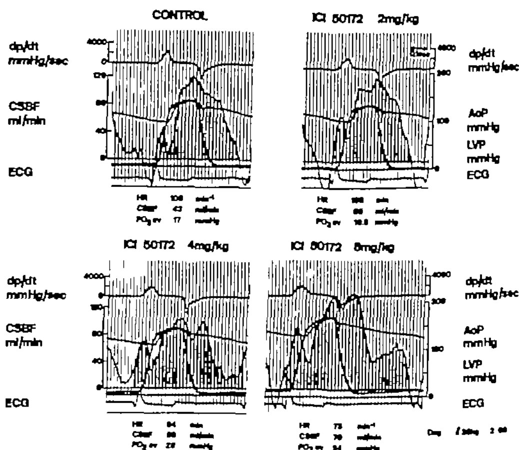


Fig. 1. Effects of ICI 50172 on hemodynamic parameters and phasic coronary sinus blood flow at spontaneous heart rhythm. The phasic coronary sinus outflow per systole is represented by the hatched area. With increasing dosage of ICI 50172, max. dp/dt decreases, CSBF and PO_2cv increase. There is an enhancement in LVEDP, LVP, and AoP following 4 and 8 mg. per kilogram. Abbreviations: *dp/dt*, Rate of left ventricular pressure rise; *CSBF*, coronary sinus blood flow; *AoP*, aortic pressure; *LVP*, left ventricular pressure; *HR*, heart rate; *PO_2cv*, coronary venous oxygen tension.

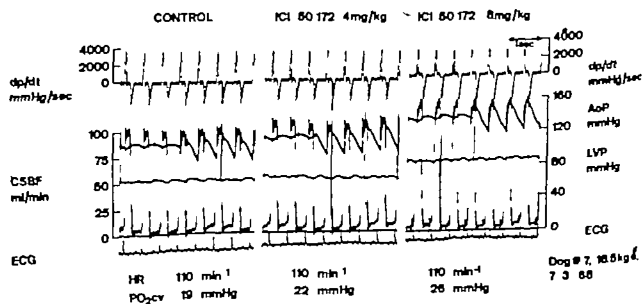


Fig. 2. Effects of ICI 50172, 4 and 8 mg. per kilogram, at constant heart rate. Left ventricular max. dp/dt decreases whereas mean CSBF and PO_2cv increase. LVP, LVEDP, and AoP rose slightly following ICI 50172. For abbreviations, see legend to Fig. 1.

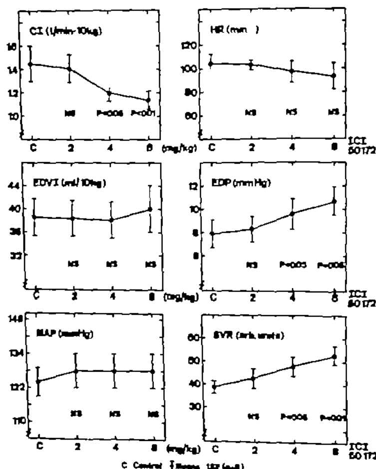


Fig 3 Hemodynamic effects of ICI 50172 in the doses of 2, 4 and 8 mg per kilogram of body weight at spontaneous heart rhythm (mean values). All P values refer to control. Following 2 mg per kilogram, no significant changes occurred. After 4 and 8 mg per kilogram, progressive decrease in CI as noted and EDP increased. SVR increased because there was no change in MAP even though the CI decreased. Abbreviations *CI* Cardiac index; *HR*, heart rate *EDVI* left ventricular end-diastolic volume index *EDP* left ventricular end-diastolic pressure; *MAP* mean aortic pressure *SVR*, systemic vascular resistance.

and by a prolongation of the interval t-dp/dt. A similar impairment of the contractile state was observed during pacing

The coronary sinus blood flow was significantly ($p < 0.05$) augmented after ICI 50172 4 mg per kilogram Since the coronary venous oxygen tension increased the A-V O decreased. The increase of CSBF together with a narrowing of the A V O indicates a primary coronary vasodilatation.[30,31] Left ventricular oxygen consumption showed no significant change At constant heart rate, PTM and PTM ESV tended to increase the augmentation of PTM ESV being significant ($p < 0.02$)

3 *Hemodynamic and coronary effects of ICI 50172 8 mg per kilogram* Again two runs were recorded as after 4 mg per kilogram one in sinus rhythm and one at constant heart rate (Tables I and II Figs 1 to 5) The trends of the hemodynamic alterations at 4 mg per kilogram became more obvious at 8 mg per kilogram At spontaneous heart rhythm the cardiac index declined whereas it remained essentially unchanged during pacing The ejection fraction fell further in both instances. Left ventricular contractility as assessed by max. dp/dt, $\frac{\text{max dp/dt}}{\text{IP}}$ and t-dp/dt

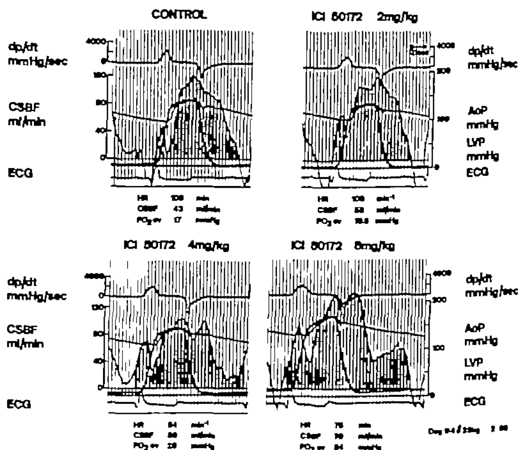


Fig 1 Effects of ICI 50172 on hemodynamic parameters and phasic coronary sinus blood flow at spontaneous heart rhythm. The phasic coronary sinus outflow per systole is represented by the hatched area. With increasing dosage of ICI 50172 max. dp/dt decreases, CSBF and PO_2cv increase. There is an enhancement in LVEDP LVP and AoP following 4 and 8 mg per kilogram Abbreviations *dp/dt* Rate of left ventricular pressure rise *CSBF* coronary sinus blood flow *AoP* aortic pressure *LVP* left ventricular pressure *HR*, heart rate PO_2cv coronary venous oxygen tension.

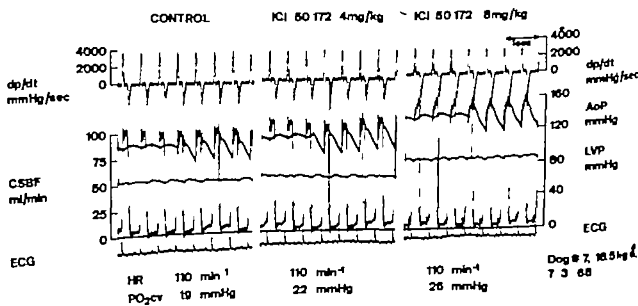


Fig 2 Effects of ICI 50172 4 and 8 mg per kilogram at constant heart rate Left ventricular max. dp dt decreases whereas mean CSBF and PO_2cv increase. LVP LVEDP and AoP rose slightly following ICI 50172 For abbreviations, see legend to Fig 1

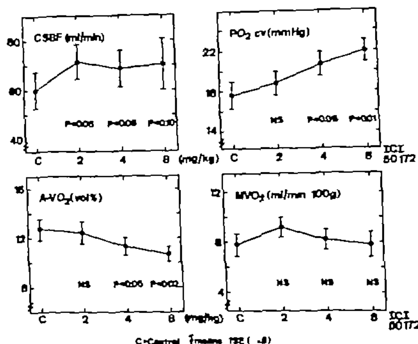


Fig 5 Coronary blood flow and left ventricular oxygen consumption following ICI 50172. The main increase in CSBF occurred already after 2 mg per kilogram. Since PO_2cv increased and A V O_2 decreased, MVO_2 remained essentially unchanged. Abbreviations. *CSBF* Coronary sinus blood flow *PO_2cv* coronary venous oxygen tension *A V O_2*, arteriovenous oxygen content difference *MVO* myocardial oxygen consumption.

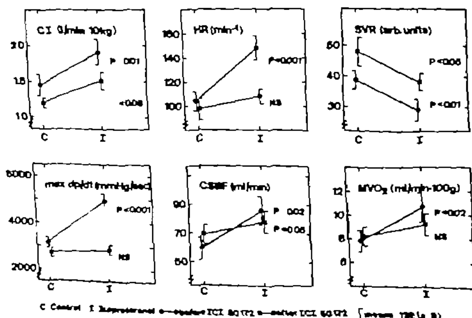


Fig 6 Hemodynamics following isoproterenol (0.034 μg per minute per kilogram) before and after ICI 50172 (4 mg. per kilogram). Heart rate and speed of left ventricular contraction (max. dp/dt) remained essentially unchanged after ICI 50172 and isoproterenol. On the other side, CI rose and SVR decreased significantly under isoproterenol before and after ICI 50172. After ICI 50172 CSBF increased following isoproterenol without change in MVO_2. Therefore, no beta-receptor blockade on coronary and peripheral vessels occurred. For abbreviations, see legends to Figs 3 4 and 5.

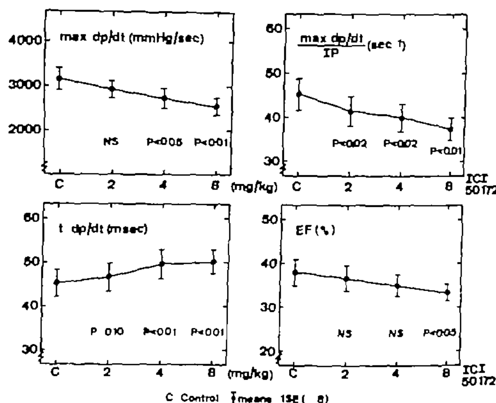


Fig 4 Effects of ICI 50172 2 4 and 8 mg per kilogram of body weight on the left ventricular contractile state and ejection fraction in sinus rhythm At 2 mg per kilogram only $\frac{\text{max. dp/dt}}{\text{IP}}$ showed a significant decrease After 4 and 8 mg per kilogram a progressive decrease in max. dp/dt, $\frac{\text{max dp/dt}}{IP}$ and EF occurred The interval from the beginning of the contraction to max. dp/dt increased Abbreviation *max dp/dt* Maximal rate of left ventricular pressure rise $\frac{max.\ dp/dt}{IP}$ contractility index *t-dp/dt* time from the beginning of contraction to max dp/dt *EF* left ventricular ejection fraction

reached the lowest level when compared with the preceding runs The systemic vascular resistance was highest at 8 mg per kilogram of ICI 50172

In the observations at constant heart rate CSBF showed a progressive increase from 64 (control) to 82 ml per minute (ICI 50172 8 mg per kilogram) Coronary vascular resistance tended to decrease At spontaneous heart rhythm an increase in CSBF occurred after 2 mg per kilogram and thereafter CSBF remained at the same level The coronary venous oxygen tension showed a progressive augmentation at both heart rhythms of about 5 mm Hg In accordance to the enhancement in PO_2cv the A V O_2 decreased significantly ($p < 0.02$) The pH was stable throughout ... MVO_2 showed no variations

At constant heart rate a further increase in PTM and PTM CSV was noted at 8 mg per kilogram as compared to the previous two runs

4 Isoproterenol before and after ICI 50172 4 mg per kilogram Isoproterenol was infused in amount of 0.034 µg per minute per kilogram Typical hemodynamic and coronary effects occurred before ICI 50172 as indicated in Table III and Fig 6 The heart rate cardiac index ejection fraction max dp dt and $\frac{\text{max dp dt}}{II}$ increased significantly Left ventricular end-diastolic pressure end-diastolic volume index ejection time t-dp dt mean aortic pressure and systemic vascular resistance decreased CSBF and MVO_2 rose (p

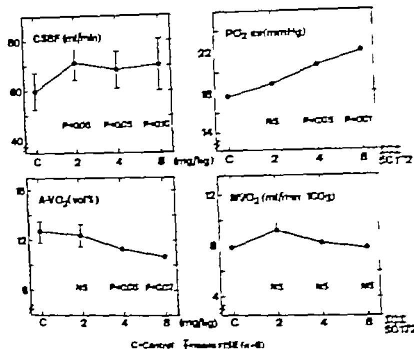


Fig. 3. Coronary blood flow and left ventricular oxygen consumption following ICI 50172. The main increase in CSBF occurred already after 2 mg per kilogram. Since PO_2cv increased and A-V O_2 decreased, MVO_2 remained essentially unchanged. Abbreviations: CSBF Coronary sinus blood flow; PO_2cv coronary venous oxygen tension; A-VO arteriovenous oxygen content difference; MVO myocardial oxygen consumption.

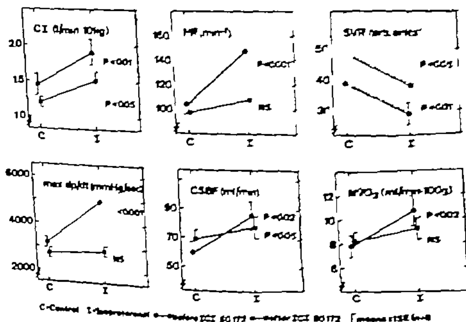


Fig. 4. Hemodynamics following isoproterenol (0.035 µg per minute per kilogram) before and after ICI 50172 (4 mg. per kilogram). Heart rate and speed of left ventricular contraction (max. dp/dt) remained essentially unchanged after ICI 50172 and isoproterenol. On the other side, CI rose and SVR decreased significantly under isoproterenol before and after ICI 50172. After ICI 50172 CSBF increased following isoproterenol without a change in MVO. Therefore, no beta-receptor blockade on coronary and peripheral vessels occurred. For abbreviations, see legend to Figs. 3, 4 and 5.

Table III *Isoproterenol (0 034 µg/min Kg) before and after ICI 50172 (4 mg/Kg)*

Dose	*CI*	*HR*	*SVI*	*EDVI*	*EF*	*LVSP*	*LVEDP*	*MAP*	*SAP*	*DAP*	*ET*
Control	1450	104	14 6	38.5	38 0	136	7.9	123	143	103	0.177
	±150	± 8	±1 5	±3 3	±3 0	± 5	±1 2	± 5	± 5	± 6	0.009
Isoproterenol 0 034 µg/ min. Kg	1917	148	13.2	31 4	42 0	138	5 1	118	143	101	0.153
	±169	±10	±1.3	±2 0	±2.8	± 7	±0 9	± 5	± 5	± 5	±0.006
p	<0 01	<0 001	<0 10	<0.01	0 05	NS	<0 01	<0.01	NS	NS	<0 01
ICI 50172 4 mg /Kg	1202	97	13.2	38 1	35 0	141	9 6	128	152	110	0 183
	± 68	± 9	±1 4	±3 1	±2.5	± 7	±1.3	± 6	± 7	± 6	±0.008
ICI 50172 4 mg./Kg + isoproterenol 0.034 µg/ min. Kg	1518	108	14 4	41 8	34 9	139	8.6	125	147	107	0.180
	±127	± 6	±1 4	±4 0	±2 0	± 6	±0.6	± 5	± 5	± 5	±0.006
p	<0.05	NS	NS	<0 05	NS	NS	NS	NS	NS	NS	NS

Abbreviations see Table I.
Body weight 22.8 ± 1.3 Kg., left ventricular weight 97 ± 8 Gm
Mean values ± 1 S.E of 8 dogs.

<0 02) Then after 4 mg per kilogram of ICI 50172 isoproterenol was infused again at the same dosage Most effects especially those upon the myocardium were abolished or reduced The changes in heart rate ejection fraction end-diastolic pressure mean aortic pressure ejection time max dp/dt $\frac{\text{max. dp/dt}}{\text{IP}}$ and MVO_2 were small and no longer significant But still cardiac index increased and systemic vascular resistance decreased Similar to the increased peripheral perfusion with reduced vascular resistance the CSBF increased and coronary vascular resistance declined (p <0 05 see Fig 6)

Discussion

Left ventricular contractility and coronary blood flow following ICI 50172 Similarly to other beta blocking compounds ICI 50172 elicits a negative inotropic effect upon the myocardium As evaluated from the changes of max dp/dt, $\frac{\text{max dp/dt}}{\text{IP}}$ and t-dp/dt, the diminution of myocardial contractility after 2 mg per kilogram is only small (Fig 4) At the higher dosages the impairment of the contractile state became more obvious. The decrease of the ejection fraction at constant heart rate together with an increase in preload and an only slight increase in afterload gives also evidence of a decrease of the inotropic state Whether the depressing effect is entirely due to the blockade of myocardial beta adrenergic activity or the compound ICI 50172 exerts per se a negative inotropic effect upon the myocardium cannot be decided from the present experiments. No studies on reserpinized animals were carried out[22] By comparing the effects of ICI 50172 with those of propranolol reported previously[22] ICI 50172 in a dose of 4 mg per kilogram has a depressing action upon the myocardial contractile state which is similar to that observed following 0 5 mg per kilogram of propranolol (decrease in max dp/dt of 13 and 11 per cent respectively)

Unlike propranolol[4,5,6] ICI 50172 augments coronary blood flow and decreases

I	M —	MHR	CSBF	CSBF/100 Gm.	PO_2cv	pH	A V O	MVO	PTM	PTM ESV	CVR	SVR
		45 3 ±3 0	39 9 ±7.5	61.0 ±8 0	17 6 ±1.3	7.309 ±0 023	12.7 ±0.9	7.8 ±0.9	2539 ±209	1 94 ±0.40	2.23 ±0.22	38.9 ±2.8
	3	40 0	85 6	92.2	21.0	7.319	11 9	10.7	3131	1.76	1 46	29 2
+	8 31	±2.5 <0 02	±9.8 <0 02	±12.8 <0 05	±1.8 NS	±0.014 NS	±0 8 NS	±1.2 <0 02	±215 <0.01	±0.26 NS	±0 12 <0 01	±3.2 <0 01
	8 1	49 7 ±3 3	68 4 ±7.3	73.1 ±7 9	20 6 ±1 2	7.323 ±0 016	11.3 ±0.7	8 2 ±0.8	2533 ±239	1 73 ±0 25	1 95 ±0 12	48 0 ±4.3
	2	47 4	77 6	82 0	20.4	7.314	11.3	9.2	2757	2.35	1.68	38.0
	19	±3 3	±7 7	±9.2	±1.2	±0 014	±0 6	±0 9	±226	±0 41	±0.11	±2.9
	25	<0.05	<0 05	<0.10	NS	NS	NS	NS	<0.10	<0 05	<0.05	0 05

slightly coronary vascular resistance. The rise in coronary flow is accompanied by an increase in coronary venous oxygen tension and by a narrowing of the coronary A V oxygen content difference (Fig 5). This particular pattern of coronary dynamics is indicative of a primary coronary vascular dilatation.[20,21] The extent of increase in flow and PO_2cv is in the order of 20 to 30 per cent and is therefore much smaller than the augmentation that occurs following a typical coronary vasodilator such as dipyridamole.[20-22]

The increase in coronary blood flow associated with a depression of myocardial contractility after ICI 50172 is a very unusual feature that is difficult to interpret. In an attempt to reconcile these two effects we will give consideration to the following hypotheses: (1) The beta receptors in the myocardium may differ from those of the coronary arteries and (2) ICI 50172 may have different actions upon the two receptor sites, i.e., a blocking effect upon the myocardial beta receptors and a stimulatory effect upon the coronary beta receptors. The assumption of two different receptor sites with different responses following ICI 50172 appears justified in view of the following experimental observations:

1. After 2 mg. per kilogram there was a significant increase in coronary blood flow with only minor effects upon left ventricular dynamics and contractility.

2. After 4 and 8 mg. per kilogram there is a definite impairment of the left ventricular contractility but coronary blood flow and PO_2cv still tended to rise and MVO remained stable. Therefore the increase in coronary blood flow cannot be attributed to the altered hemodynamics. Whereas the diminution of the contractile state is explained by the blockade of the myocardial beta receptors, the augmentation of CSBF is incompatible with the idea of blocked coronary beta receptors. On the contrary some coronary vasodilatation took place that was probably mediated by a direct stimulatory effect of ICI 50172 upon the coronary beta-adrenergic receptors.

3. Isoproterenol given after 4 mg. per kilogram of ICI 50172 is no longer effective in increasing left ventricular contractility

Table III *Isoproterenol (0.034 μg/min Kg) before and after ICI 50172 (4 mg/Kg)*

Dose	*CI*	*HR*	*SVI*	*EDVI*	*EF*	*LVSP*	*LVEDP*	*MAP*	*SAP*	*DAP*	*ET*
Control	1450 ±150	104 ± 8	14.6 ±1.5	38.5 ±3.3	38.0 ±3.0	136 ± 5	7.9 ±1.2	123 ± 5	143 ± 5	103 ± 6	0.177 0.009
Isoproterenol 0.034 μg/min. Kg	1917 ±169	148 ±10	13.2 ±1.3	31.4 ±2.0	42.0 ±2.8	138 ± 7	5.1 ±0.9	118 ± 5	143 ± 5	101 ± 5	0.153 ±0.007
p	<0.01	<0.001	<0.10	<0.01	0.05	NS	<0.01	<0.01	NS	NS	<0.01
ICI 50172 4 mg/Kg	1202 ± 68	97 ± 9	13.2 ±1.4	38.1 ±3.1	35.0 ±2.5	141 ± 7	9.6 ±1.3	128 ± 6	152 ± 7	110 ± 6	0.183 ±0.008
ICI 50172 4 mg/Kg + Isoproterenol 0.034 μg/min. Kg	1518 ±127	108 ± 6	14.4 ±1.4	41.8 ±4.0	34.9 ±2.0	139 ± 6	8.6 ±0.6	125 ± 5	147 ± 5	107 ± 5	0.190 ±0.006
p	<0.05	NS	NS	<0.05	NS	NS	NS	NS	NS	NS	NS

Abbreviations see Table I.
Body weight 22.8 ± 1.3 Kg., left ventricular weight 97 ± 8 Gm
Mean values ± 1 S.E. of 8 dogs.

<0.02). Then after 4 mg per kilogram of ICI 50172 isoproterenol was infused again at the same dosage. Most effects, especially those upon the myocardium, were abolished or reduced. The changes in heart rate, ejection fraction, end-diastolic pressure, mean aortic pressure, ejection time, max dp/dt, $\frac{\text{max. dp/dt}}{\text{IP}}$ and MVO_2 were small and no longer significant. But still cardiac index increased and systemic vascular resistance decreased. Similar to the increased peripheral perfusion with reduced vascular resistance, the CSBF increased and coronary vascular resistance declined (p <0.05, see Fig 6).

Discussion

Left ventricular contractility and coronary blood flow following ICI 50172. Similarly to other beta blocking compounds, ICI 50172 elicits a negative inotropic effect upon the myocardium. As evaluated from the changes of max dp/dt, $\frac{\text{max. dp/dt}}{\text{IP}}$ and t-dp/dt, the diminution of myocardial contractility after 2 mg per kilogram is only small (Fig 4). At the higher dosages the impairment of the contractile state became more obvious. The decrease of the ejection fraction at constant heart rate together with an increase in preload and an only slight increase in afterload gives also evidence of a decrease of the inotropic state. Whether the depressing effect is entirely due to the blockade of myocardial beta adrenergic activity or the compound ICI 50172 exerts per se a negative inotropic effect upon the myocardium cannot be decided from the present experiments. No studies on reserpinized animals were carried out.[22] By comparing the effects of ICI 50172 with those of propranolol reported previously,[22] ICI 50172 in a dose of 4 mg per kilogram has a depressing action upon the myocardial contractile state which is similar to that observed following 0.5 mg per kilogram of propranolol (decrease in max dp/dt of 13 and 11 per cent respectively).

Unlike propranolol[...] ICI 50172 augments coronary blood flow and decreases

anisms from the carotid sinus resulting in an increased sympathetic discharge to the heart and the peripheral vessels. The response to the adrenergic stimulation in the peripheral vasculature is essentially vasoconstrictive since there is a predominance of the constrictive alpha receptors over the dilating beta receptors.[30] In the myocardium no effect is to be expected from the increased sympathetic discharge because the inotropic and chronotropic beta-receptor sites are blocked by ICI 50172. Whether an increased sympathetic outflow to the heart in the absence of hemodynamic changes sufficient to alter myocardial oxygen consumption can directly influence the coronary vascular resistance is still a matter of debate.[31,32]

Myocardial oxygen consumption. The two major determinants of oxygen consumption are the contractile state and the wall tension.[33,34] In order to evaluate the course of the two determinants, throughout the study the index of contractility

$$\left(\frac{max.\ dp/dt}{IP}\right)^{22}$$ and the product of PTM ESV[19] used to represent left ventricular contractile state and tensile stress, respectively, were plotted in Fig. At increasing the dose of ICI 5017 there is a progressive decrease of the index of contractility and a progressive increase in tensile stress. These changes of the two determinants of MVO going in opposite directions, may explain why essentially no changes in MVO were observed throughout the study.

In summary, ICI 50172 is a unique compound within the family of beta blocking agents since it blocks myocardial but not coronary and peripheral vascular adrenergic beta receptors. In the treatment of angina pectoris it may be particularly useful because it protects the heart against excessive sympathetic drive and induces mild coronary vascular dilatation.

Summary

The hemodynamic and coronary effects of the beta-blocking agent, ICI 50172 were assessed in the closed-chest dog. At increasing dosages of the drug from 2 to 8 mg. per kilogram there was a progressive impairment of left ventricular contractility as evaluated by a decrease of max. dp/dt

$$\frac{max.\ dp/dt}{IP}$$ and the ejection fraction. Left ventricular coronary flow, which was determined by an electromagnetic flow probe catheter inserted into the coronary sinus, rose up to 30 per cent above the control level following ICI 50172. This increase was accompanied by a rise of coronary venous oxygen tension reflecting primary coronary vasodilatation. Left ventricular oxygen consumption remained unchanged. Isoproterenol administered after 4 mg. per kilogram of ICI 50172 produced neither an increase in heart rate nor an enhancement of the speed of left ventricular contraction. Systemic vascular resistance, however, fell following isoproterenol to a similar extent before and after ICI 50172. Therefore the myocardial beta receptors were blocked, whereas the peripheral beta receptors appeared not to be influenced by the drug.

The fact that ICI 50172 abolished the positive chronotropic and inotropic effects of isoproterenol and increased coronary blood flow without an altered myocardial oxygen consumption lends strong support to the hypothesis that there exist two different beta-receptor sites within the myocardium and in the coronary vasculature. It is assumed that ICI 50172 has a direct stimulatory influence upon the coronary beta receptors resulting in a mild vasodilatation of the coronary bed.

The authors are indebted to Mrs. Doris Maocch and Miss Ursula Rang for technical assistance and to Miss Margrit Baer and Mr. Elisabeth Wicker for careful secretarial work.

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This is proof that myocardial beta receptors are blocked Under the same conditions isoproterenol enhanced CSBF without a significant variation of the myocardial oxygen consumption These findings lend strong support to the hypotheses that there must be different beta receptor sites in the myocardium and in the coronary vasculature and that ICI 50172 has different actions upon the myocardial and the coronary beta receptor sites

Myocardio-selective action of ICI 50172 It has been demonstrated that ICI 50172 has no or little effect upon the beta receptors located in the peripheral vasculature[7,28] and in the muscles of the bronchi[7] With respect to the action of ICI 50172 upon the beta receptor activity of the peripheral vascular tree our results agree with those of Dunlop and Shanks[7] Following isoproterenol before and after 4 mg per kilogram of ICI 50172 the decrease of the systemic vascular resistance was nearly the same (27 and 21 per cent respectively) This means that after ICI 50172 stimulation of beta receptors of the peripheral vessels (vasodilatation) is still possible

ICI 50172 abolishes the cardiodynamic effects of isoproterenol except the augmentation of coronary blood flow If one accepts the hypothesis of dual cardiac beta receptor sites i e myocardial and coronary one can conclude that the cardio-selective action of ICI 50172[9] is limited to a blockade of the myocardial beta receptors Then the term myocardio-selective beta blockade would be more appropriate than cardio-selective beta blockade

Increase in systemic vascular resistance following ICI 50172 In view of the vasodilatory effects of ICI 50172 upon the coronary vascular bed one may expect a similar action upon the peripheral vasculature An increase of the systemic vascular resistance however occurred (Fig 3) The mechanism of this vasoconstriction is thought to be the result of an enhanced sympathetic discharge originating from the baroreceptors. The negative inotropic effect of ICI 50172 leads to a decrease of cardiac output and diminishes the rate of pressure change within the arterial tree. Both variations may initiate reflex mech

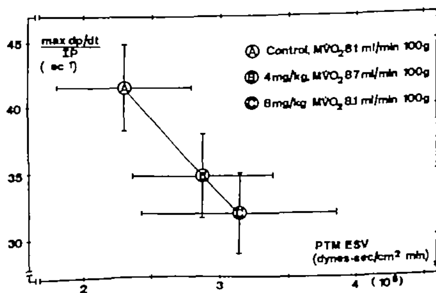


Fig 7 Left ventricular contractility and tensile stress following ICI 50172 at constant heart rate. Under ICI 50172, contractility as evaluated by $\frac{\text{max. dp/dt}}{\text{IP}}$ decreased and tensile stress evaluated by PTM ESV increased. Then the two major determinants of MVO varied in opposite directions. This explains why MVO_2 remained more or less unchanged under ICI 50172 Abbreviation $\frac{max\ dp/dt}{IP}$ Contractility index *PTM ESV* pressure-time per minute multiplied by end-systolic volume

Vectorcardiographic criteria for the diagnosis of left ventricular hypertrophy

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Current vectorcardiographic (VCG) criteria for the diagnosis of left ventricular hypertrophy (LVH) are based mainly on an increase in the magnitude of the maximum QRS vector (MQV) [1-4] However separation of hypertrophied from nonhypertrophied hearts by voltage criteria alone is limited by overlap in this measurement between the two groups. Attempts to improve sensitivity of the criteria by reducing the amplitude of voltage required necessarily result in lowered specificity while gains in specificity achieved by increasing the amplitude of voltage required must be made at the expense of sensitivity

Changes in various instantaneous vectors other than the MQV also occur in LVH altering the QRS loop configuration[1-4] (Fig 1) To the extent that these changes are independent of the magnitude of the MQV and different from normal their use should improve the diagnosis of LVH over the use of the magnitude of the MQV alone

The purpose of this study was to define criteria for the diagnosis of LVH based on changes in these other QRS vectors as well as on the increase in magnitude of the MQV

Methods and materials

Criteria were developed by contrasting the vectorcardiograms of 200 normal controls and 100 patients with clinical evidence of pure LVH They were then tested on 100 consecutive autopsied cases.

The control group consisted of healthy adults who were normal by history physical examination electrocardiogram (ECG) and chest x ray The mean age was 39 (range 18 to 69) with approximately 25 per cent of the subjects in each decade starting at age 20 There were 196 males and 4 females.

The 100 patients with LVH were selected from the wards and clinics of the Cincinnati General Hospital They were included for study if they had a disease known to produce LVH and at least one of the following clinical evidences of LVH (1) unequivocal physical signs (2) x-ray evidence or (3) typical ECG findings with both voltage (Table 1) and ST T changes of LVH Eighty per cent of the patients

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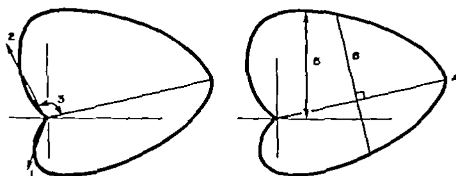


Fig 3. Transverse plane QRS measurements used in forming additional QRS criteria. 1 Direction of the initial deflection. 2, Direction of the terminal deflection. 3 Angle between the direction of the MQV and that of the terminal deflection. 4 Time of inscription of the MQV 5 Maximum posterior force. 6 Line which separates the QRS loop int distal and proximal QRS loop areas

selected as the basis for the additional QRS criteria (Fig 3)

a. The direction of the initial deflection This was defined as the line joining the O point to the midpoint of the initial deflection The initial deflection includes the segment of the loop from its origin to the point of maximal curvature of the initial portion of the QRS loop

b The direction of the terminal deflection. This was defined as the line joining the J point to the midpoint of the terminal deflection. The terminal deflection includes the segment of the loop from the point of maximal curvature of the terminal portion of the QRS loop to the J point. In cases in which the junction of the afferent limb of the QRS loop and terminal deflection were not apparent (the segment of loop between the MQV and J point was either straight or formed an arc with constant curvature) the mid point on the loop between the MQV and J point was used as the onset of the terminal deflection.

c. The angle between the direction of the MQV and the direction of the terminal deflection The angle was considered positive when th terminal deflection was counterclockwise to the MQV and negative when clockwise

d. The time of inscription of the maximum QRS vector

e. The maximum posterior force. This was defined as the distance in millivolts from the 0 to 180 degree axis to the most posterior point of the QRS loop

f A comparison of the sizes of the distal and proximal (with respect to the O point) QRS loop areas. These two areas were formed by dividing the QRS loop with a line which bisected and was perpendicular to the MQV An estimate of which area was greater could be made without error by simple inspection in the great majority of cases. When the decision was difficult, planimeter readings were obtained and usually showed the areas to be equal.

3 S-T and T criteria were based on the direction of the S-T and maximum T vectors in the transverse plane. The 22 patients in the LVH group receiving digitalis were not used in determining these criteria.

Values for the additional QRS and ST T criteria were chosen so that each criterion was met in less than 5 per cent of the normal group Combinations of these criteria with the voltage criteria were then selected which provided optimal separation of the normal and LVH groups.

The resulting methods of diagnosis of LVH were then applied to a series of 100 consecutive autopsied cases which had VCGs recorded within 6 months of death (all but 4 were recorded within 4 months) Cases with a QRS loop duration of 0 12 second or more were excluded Anatomic hypertrophy was defined using Dower's modification[11] of Zeek's criteria. If hyper

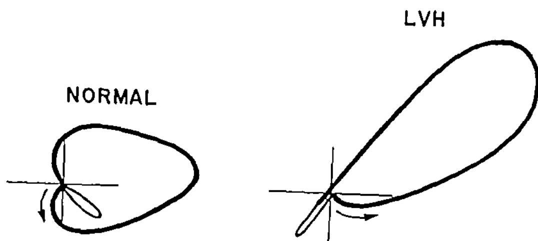


Fig 1 Diagrammatic representation of the transverse plane QRS loop in LVH compared with that of the normal individual. In addition to the increase in magnitude of the maximum QRS vector in LVH the QRS loop configuration differs from normal.

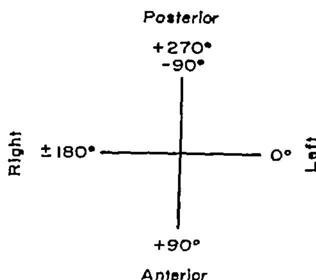


Fig 2 Reference frame for angular notation, transverse plane.

had physical signs 76 per cent had x ray evidence and 62 per cent had both QRS and ST T changes of LVH Conditions which excluded cases from the clinical LVH group were (1) history or findings of right ventricular failure (2) more than one episode of left ventricular failure in the past (3) clinical evidence of left ventricular failure at the time of recording (4) clinical evidence of coronary artery disease unless angina was adequately explainable on another basis (5) ECG evidence of conduction abnormalities (6) ECG signs of myocardial infarction (the presence of a QS in Leads V_1 and V_2 or a large Q in Leads II III or aV_F without a history suggestive of coronary artery disease was not a reason for exclusion) and (7) other disease which may alter the ECG and VCG such as chronic obstructive lung disease The diseases which caused the LVH were hypertension in 65 patients aortic stenosis in 13 aortic insufficiency in 13 mitral insufficiency in 2 and combinations of these in 7 The mean age of the LVH group was 47 (range 18 to 76) There were 52 men and 48 women

The VCG s were recorded using the Frank lead system The subjects were supine and the chest electrodes were placed at the level of the fifth intercostal space at the sternal margin The reference frame for angular notation is shown in Fig 2

Three sets of criteria were developed (1) QRS voltage criteria (2) additional QRS criteria and (3) ST T criteria

1 The voltage criteria were based on the magnitude of the planar projections of the maximum spatial QRS vector in the transverse and frontal planes. In most cases these are equivalent to the maximum planar QRS vectors Separate values were determined for subjects under age 40 and those age 40 or older

2 Various measurements of the QRS loop were made that had possible value in separating the normal subjects from cases with hypertrophy Six of these in the transverse plane which effected the best separation and were easy to perform were

Table III Additional QRS criteria transverse plane

Criteria	Percentage of cases which met criterion	
	Normal (200 cases)	Clinical LVH (100 cases)
Both initial and terminal deflections directed leftward	3	33
Direction of terminal deflection anterior to −65 degrees	4.5	26
Angle between MQV and terminal deflection < +35 degrees	2.5	29
Time of inscription of MQV > 0175 sec	4	32
Maximum posterior force > 1.2 mv	4	63
Distal area > proximal area	0.5	19

Table IV S-T and T criteria transverse plane

Criteria	Incidence and percentage of cases which met criterion	
	Normal	Clinical LVH
S-T vector directed between +120 and +270 degrees	5/167 (3%)	48/73 (66%)
Maximum T vector directed between +70 and +270 degrees	1/200 (0.5%)	54/75 (72%)

Table V Accuracy of methods in the diagnosis of LVH

Method	Incidence of positive diagnoses (%)			
	Clinical series		Autopsy series	
	Normal (200 cases)	LVH (100 cases)	N LVH (34 cases)	LVH or CVH (66 cases)
A (QRS voltage criteria)	3	75	11.7	33.3
B (Additional QRS criteria)	1	9	0	16.6
C (S-T or T plus additional QRS criteria)	0	4	3	0
A and B	4	84	11.7	50
A, B and C	4	88	14.7	50

the sensitivity and increased the number of false positives by one case.

One or more of the ECG voltage criteria were met in 27 (40.9 per cent) of the 66 ay cases with LVH or CVH and in 8 per cent) of the 34 cases without

Discussion

Voltage criteria for the diagnosis of LVH The voltage criteria values determined from the present normal control series agree quite closely with the upper ninety-sixth percentile values found in 518 normal men by Pipberger and associates.[15] Romhilt

Table I ECG voltage criteria for the diagnosis of LVH

R in Lead I plus S in Lead III >25 mm.
S in aV_R >14 mm.
R in aV_L >11 mm.
R in aV_F >20 mm.
S in V_1 plus R in V_5 or V_6 >35 mm
R in V_5 or V_6 >26 mm.

Table II Maximum QRS-vector magnitudes (mv) in transverse and frontal planes of the 200 normal controls

Age group	Transverse plane		Frontal plane	
	Upper 97.5 percentile	Mean	Upper 97.5 percentile	Mean
Under age 40	2 0	1 3	2 4	1 6
Age 40 and over	1 9	1 3	2 0	1 4

trophy was present it was designated LVH when the LV wall thickness was 13 mm or more and right ventricular hypertrophy (RVH) when the RV wall thickness was 5 mm or more (4 mm or more if RV dilatation was present) Combined ventricular hypertrophy (CVH) was considered present if both ventricular walls were thick by these criteria. There were 22 patients with LVH 44 with CVH 6 with RVH and 28 with no hypertrophy The mean heart weight and heart weight/body length index of the cases with LVH and CVH were 546 grams and 3 21 grams per centimeter respectively The mean age of the autopsy group was 59 (range 17 to 92) There were 60 men and 40 women

For comparison purposes 6 ECG voltage criteria (Table I) were applied to the electrocardiograms (taken at the same sitting as the VCG s) of the autopsy series.

Results

QRS voltage criteria The upper 97 5 percentiles of the magnitude of the MQV in the transverse and frontal planes of the normal series were used for the voltage criteria (Table II) To prevent a false diagnosis of LVH in cases of RVH which have a large MQV directed rightward it was required that this vector be directed leftward to make a diagnosis of LVH The mean magnitude of the MQV in the clinical LVH group was 2 4 mv in the transverse plane and 2 25 mv in the frontal plane

Additional QRS criteria The values selected for the additional QRS criteria and their individual capacity to separate the cases of LVH from the normal subjects are shown in Table III

ST and T criteria The values chosen for the ST T criteria are shown in Table IV

The following methods for application of the criteria in the diagnosis of LVH were used In all methods an additional requirement was that the MQV be directed leftward

METHOD A LVH is present if QRS voltage criteria are met in either the transverse or frontal plane

METHOD B If QRS voltage criteria are not met LVH is present if any two additional QRS criteria are met providing the magnitude of the MQV exceeds the normal mean in either the transverse or frontal plane (Table II)

METHOD C LVH is present as in method B except an S T or T criterion may replace one (only) additional QRS criterion

The accuracy of these methods and their combinations are shown in Table V In the clinical series the voltage criteria were met by 75 per cent of the LVH group and 3 per cent of the normal subjects By using the additional QRS criteria as well (Methods A and B) the diagnostic sensitivity increased to 84 per cent while the incidence of false positives increased to 4 per cent The addition of S-T and T criteria (Methods A B and C) increased the sensitivity to 88 per cent with no further increase in the incidence of false positives

In the autopsy series voltage criteria alone recognized 22 (33 3 per cent) of the 66 cases with LVH or CVH and falsely diagnosed 4 (11 7 per cent) of the 34 cases without LVH The use of the additional QRS criteria increased the recognition rate to 50 per cent of the cases with LVH or CVH with no increase in the incidence of false positives Method C did not change

Table III Additional QRS criteria transverse plane

Criteria	Percentage of cases which met criterion	
	Normal (200 cases)	Clinical LVH (100 cases)
Both initial and terminal deflections directed leftward	3	33
Direction of terminal deflection anterior to −65 degrees	4 5	26
Angle between MQV and terminal deflection < +35 degrees	2 5	29
Time of inscription of MQV > .0475 sec.	4	32
Maximum posterior force > 1.2 m	4	63
Distal area > proximal area	0 5	19

Table IV S-T and T criteria transverse plane

Criteria	Incidence and percentage of cases which met criterion	
	Normal	Clinical LVH
S-T vector directed between +120 and +270 degrees	5/167 (3%)	48/73 (66%)
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Table V Accuracy of methods in the diagnosis of LVH

Method	Incidence of positive diagnoses (%)			
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A (QRS voltage criteria)	3	75	11 7	33 3
B (Additional QRS criteria)	1	9	0	16 6
C (S-T or T plus additional QRS criteria)	0	4	3	0
A and B	4	84	11 7	50
A, B and C	4	88	14 7	50

the sensitivity and increased the number of false positives by one case

One or more of the ECG voltage criteria were met in 27 (40 9 per cent) of the 66 autopsy cases with LVH or CVH and in 3 (8.8 per cent) of the 34 cases without LVH

Discussion

Voltage criteria for the diagnosis of LVH The voltage criteria values determined from the present normal control series agree quite closely with the upper ninety-sixth percentile values found in 518 normal men by Pipberger and associates.[9,11] Romhilt

and associates[3] using these latter values as upper limits of normal found an incidence in an autopsy series of 61 per cent correct diagnoses in 70 cases with LVH and no false positives in 23 cases without LVH This is a significantly higher degree of accuracy than was obtained in the present autopsy series using very similar voltage criteria. Part of the greater sensitivity found in that series may be due to the fact that the mean heart weight of hypertrophied hearts was greater (595 grams compared to 546 grams in the present series) and 7 cases of complete left bundle branch block were included while such cases were excluded in this series The results with voltage criteria in the present series agree more closely with the results in a recent larger autopsy series[1] in which the incidence of diagnosis was 41 7 per cent of 103 cases with LVH and 11 4 per cent of 61 cases without hypertrophy (per cents calculated from graph data) using the normal upper ninety fifth percentile of the transverse plane projection of the maximum spatial QRS vector The value of this measurement in the latter series was 1 59 mv however which is considerably lower than the value used in the present series.

Frontal plane voltage criteria were used in addition to transverse plane–voltage criteria in order to recognize increases in QRS magnitude in cases which have a more or less vertical axis. While no additional case in the autopsy series was diagnosed by their use three cases in the clinical LVH group exceeded the upper limits of normal in the frontal plane only

Several factors appear to have contributed to the greater accuracy of the voltage criteria in the clinical series compared to the autopsy series. First coronary artery disease was excluded from the clinical series while 15 of the 66 autopsy cases had myocardial infarctions. The mean transverse plane MQV of these 15 cases was 1 53 mv compared to 1.89 mv in a group without infarction that was matched by heart weight per body length index. Second the mean age of the clinical LVH series (47 years) was less than that of the autopsy cases of LVH or CVH (56 7 years) and it is known that the magnitude of QRS forces tends to decrease with increasing age.[12] Third the degree of hypertrophy was probably greater in the clinical than in the autopsy group Clinical evidence of LVH was present in every clinical case while 20 per cent of the autopsy cases with LVH and CVH had no such evidence

Additional QRS criteria That parameters of the QRS loop other than the magnitude of the MQV may be helpful in recognizing LVH has been suggested previously[9,10] Mazzoleni and associates,[9] using the cube-lead system described multiple QRS loop magnitude measurements one of which the maximum posterior force was used in this study The time of occurrence of the MQV has been shown to increase with increases in the left ventricular peak systolic pressure[9] The sum of the magnitude of the spatial MQV and several adjacent vectors improved the detection of cases with left ventricular overload over the use of the spatial MQV alone[4]

The tendency to posterior displacement of the MQV in LVH[3,4] was not sufficiently pronounced in the present series to be useful alone A cutoff point which included 5 per cent of the normal subjects (posterior to −55 degrees in the transverse plane) included only 12 per cent of the LVH group However the tendency to posterior displacement was made use of indirectly in the criterion based on the angle between the MQV and the terminal deflection Superior deviation of the MQV which tends to occur in LVH was not used as one of the criteria in the present study because of its more basic association with myocardial fibrosis.[13,14]

While none of the additional QRS criteria were as efficient as the voltage criteria on their own they were able to effect a reasonable separation of the normal and clinical LVH cases. The incidence of cases which had a leftward MQV and met two additional QRS criteria regardless of the magnitude of the MQV was ? per cent in the clinical normal group and 55 per cent in the clinical LVH group In the autopsy group the degree of hypertrophy appeared to be related to the number of additional QRS criteria met (Fig 4) There was a significantly greater mean heart weight per body length index in cases which

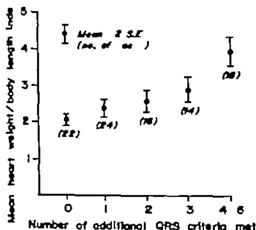


Fig 4 Relationship of heart weight per body length index to number of additional QRS criteria met in autopsy cases with LVH, CVH or no hypertrophy

met 4 or more criteria than in those which met fewer criteria ($p < 001$)

The proposed use of the additional QRS criteria in the diagnosis of LVH was directed primarily towards improving sensitivity They were applied to cases that did not meet voltage criteria and would otherwise be considered false negatives. Two conditions were attached to their use in order to prevent a concomitant decrease in specificity First, the stipulation of a less strict voltage requirement was used to prevent false diagnosis in cases of emphysema in which there is a tendency to posterior displacement of the QRS loop but in which there is also a tendency to reduction in QRS magnitude. The normal mean of the magnitude of the MQV was chosen for this purpose primarily because 97 per cent of the LVH group exceeded it in either the transverse or frontal plane Second, it was required that two additional QRS criteria be met (Method B) rather than only one. As a result, in the clinical series only 1 per cent of the normal subjects were falsely diagnosed by the use of the additional QRS criteria (Method B) while in the autopsy series there was no increase in the incidence of false positives as a result of their use. However two of the four cases that were false positives by QRS voltage criteria in the autopsy series did meet two or more additional QRS criteria

Distortion of the QRS loop by disease processes other than LVH so that one or more of the additional QRS criteria would be met is a definite possibility The incidence of cases which met two or more additional QRS criteria and had a leftward MQV was higher in the 34 autopsy cases without LVH or CVH (20 6 per cent) than in the 200 normal cases in the clinical series (2 per cent) It was the stipulation that the MQV magnitude exceed the normal mean which prevented these cases from being added to the number of false positives resulting from the use of QRS voltage criteria.

Another potential use of the additional QRS criteria is to confirm the diagnosis of LVH in cases which meet voltage criteria. The need for additional signs is suggested by the absence of clinical evidence of heart disease in 5 to 39 per cent of cases which meet ECG voltage criteria similar to those used in this study[11] An advantage of QRS over S-T and T changes in this regard is that common factors such as myocardial ischemia and digitalis which may produce a left ventricular strain pattern are not known to alter the QRS-loop configuration. In the clinical normal series, 4 of the 6 false positives by VCG voltage criteria could be eliminated by requiring at least one additional QRS criterion, and in the autopsy series 5 of the 7 false positives (4 by VCG voltage and another 3 by ECG criteria) could be eliminated by requiring at least 2 additional QRS criteria. However these gains in specificity would be associated with decreased sensitivity in that similar maneuvers applied to the cases with LVH would reduce the recognition rate from 84 to 76 per cent in the clinical series and from 50 to 45 per cent in the autopsy series.

S-T and T criteria The high degree of sensitivity of criteria based on S-T and T changes described in other reports was confirmed.[4] Because of their poor specificity they were used in the diagnosis of LVH only if at least one additional QRS criterion was met as well (Method C) As expected they were more helpful in separating cases of LVH from clinically normal subjects than from unselected autopsy

cases without LVH in which other abnormalities were not excluded

VCG versus ECG The accuracy of the VCG in the diagnosis of LVH has been found to be greater[9,11] the same,[1,2] and less[10] than that of the ECG Part of the discrepancy between various reports relates to differences in the actual values of criteria that are compared In this autopsy series the ECG voltage criteria were more accurate (40 9 per cent correct positives 8.8 per cent false positives) than the VCG voltage criteria (33 3 per cent correct positives, 11 7 per cent false positives) The use of electrocardiographic evidence for admission to the clinical LVH group precluded a meaningful comparison in the clinical series.

That ECG and most current VCG criteria could yield similar results is not surprising in that both are based primarily on the increase in QRS size Information concerning changes in the spatial relationships between various QRS vectors which occur in LVH is not readily available from the scalar ECG because of its single dimensional display of QRS forces. The VCG on the other hand delineates these changes well and by using them in addition to voltage criteria in the present autopsy series the sensitivity of the VCG (50 per cent) was greater than the ECG (40 9 per cent)

Summary

Increased voltage is only one of several electromotive changes that occur in left ventricular hypertrophy (LVH) The purpose of this study was to improve the vectorcardiographic diagnosis of LVH by defining criteria based on other QRS changes as well They were determined by contrasting the VCG s of 200 normal subjects with those of 100 patients who had clinical evidence of pure LVH and subsequently were tested on 100 consecutive autopsied cases. Voltage criteria were formed using the magnitude of the maximum QRS vector while additional QRS criteria were developed using the following characteristics of the transverse plane QRS loop found in LVH leftward displacement of the initial and terminal deflections increased magnitude of posteriorly directed vectors prolongation of the time of inscription of the maximum QRS vector and enlargement of the distal portion of the QRS loop relative to the proximal portion S-T and T criteria were also determined When tested on the autopsy series the 33 3 per cent recognition rate achieved with voltage criteria was increased to 50 per cent with the use of the additional QRS criteria with no increase in the incidence of false positives. The additional QRS criteria were also shown to be useful in confirming the diagnosis of LVH made by voltage criteria

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Left ventricular function during the early and late stages of scar formation following experimental myocardial infarction*

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The trend toward earlier ambulation following acute myocardial infarction (MI) and more recently the advocacy of exercise programs later in the management of such patients indicate the importance of evaluating the functional adequacy of the infarcted left ventricle at various stages of healing The sequential gross and histopathologic changes of such lesions have previously been described in man[1] and in the experimental animal[2]

Attempts to evaluate hemodynamics following acute coronary ligation in the dog have been hampered by complicating arrhythmias, a high mortality rate short study periods, and the need for thoracotomy[3,4] Studies performed a few days to 2 or 3 weeks later have avoided the problem of immediate death but have also involved thoracotomy for coronary artery ligation and/or the acquisition of data and have touched only tangentially upon the evaluation of left ventricular (LV) function[5-7]

The ability to induce MI by thrombus via a catheter electrode in the closed-chest dog and the development of methods for comprehensive evaluation of LV function in this preparation permitted study during the early and late stages of scar formation following MI avoiding the aforementioned disadvantages

Methods

Myocardial infarction (MI) was produced experimentally under sterile conditions in 19 closed-chest anesthetized dogs A modification of the method of Salazar was used in which a thrombus was produced by means of an electrode catheter introduced through the left common carotid artery into either the circumflex or anterior descending branch of the left main coronary artery[8] The mortality rate

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from ventricular arrhythmias, despite drug therapy is approximately 40 to 50 per cent with this method for producing MI in our laboratory. Of the survivors 7 dogs were studied 3 to 4 weeks later (Group A early scar formation stage), 12 dogs were studied 6 to 8 weeks after MI (Group B late scar formation stage). Ten normal dogs served as controls.

Healthy mongrel dogs were anesthetized with morphine sulfate (3 mg. per kilogram) and sodium pentobarbital (15 to 20 mg. per kilogram) and placed in the right lateral decubitus position. Cuffed endotracheal tubes were inserted and respiration was assisted by means of a Harvard respiration pump to assure adequate ventilation.[9] Frequent arterial pH determinations were performed throughout the study period to confirm maintenance of the physiologic range. An 80 cm. No. 7 NIH or Goodale-Lubin catheter was passed retrograde via the right femoral artery to the apex of the left ventricle (LV). A 50 cm. No. 6 NIH catheter was advanced to the aortic root 1 to 2 cm. above the aortic valve via the right common carotid artery. A small polyethylene catheter (PE 60) was introduced into the left external jugular vein and advanced to the right atrium for infusion of angiotensin. Arterial hematocrit was determined in duplicate by the microhematocrit method to assure comparable normal values in the three groups studied.

Measurement was made of heart rate, LV end-diastolic pressure (LVEDP), aortic pressure, cardiac output (CO), and LV end-diastolic volume (EDV) before and during continuous graded infusions of angiotensin, 2.5 μg per milliliter of normal saline,[18] sufficient to raise aortic diastolic pressure in approximately 10 mm. Hg increments above control level. Following an initial stable blood pressure response to angiotensin (5 to 7 minutes), hemodynamic measurements were performed. In several instances (Normal group 1 dog, Group A 3 dogs, Group B 5 dogs) following a first angiotensin run, 30 to 60 minutes were allowed to elapse for achievement of a new control state and another infusion was then performed. For purposes of statistical analysis, two levels of afterloading were distinguished: 10 to 20 mm. Hg elevation in aortic diastolic pressure (AI) and 21 to 40 mm. Hg elevation in aortic diastolic pressure (AII). The few instances in which an elevation above 40 mm. Hg occurred were not subjected to statistical analysis.

Statham pressure transducers were used for measurement of LV (P23Gb) and aortic (P23Db) pressures. These were placed at midthoracic level, balanced for equal sensitivity, and adjusted so that when recorded a 1 mm. deflection was approximately equal to 1 mm. Hg. LVEDP was measured from records obtained at a sensitivity three times higher. Maximal rate of LV pressure rise (MRPR) was obtained using a resistance-capacitance differentiating circuit (time constant, 1.1 msec.) connected to the output of the left ventricular pressure channel. The maximum error of the differentiator is approximately 0.9 per cent when summing the fundamental with the tenth harmonic.[13] The response characteristics of this system have been found to be satisfactory by other workers.[13] Systolic ejection period (SEP) was obtained from superimposed aortic and LV pressure pulses. By use of an integrator channel triggered by the R wave of the electrocardiogram (ECG) LV pressure-time during each cycle was integrated electrically and tension time index (TTI)[14] was measured as the integral over the period of ejection. Mean LV systolic pressure during ejection (LVS) was obtained by dividing TTI by SEP.

CO and EDV were determined by dye dilution. CO was measured in duplicate or triplicate for each stage of the study by the continuous infusion method[15] using indocyanine green (1.0 mg. per milliliter) at infusion rates of 7 or 15 ml. per minute into the LV and sampling at the aortic root. This method has been shown in this laboratory to have excellent reproducibility and to yield output measurements insignificantly different from those obtained with sudden injections into the pulmonary artery. Stroke volume (SV) was obtained by dividing CO by heart rate obtained from the ECG during inscription of dye curves. Cardiac index (CI) was obtained by dividing CO by the

weight in kilograms. The technique for LV volume measurement has been described previously[17] In the present study green dye (1 to 3 ml) was injected rapidly into the LV and blood sampled with Harvard pumps at 1 5 to 2 0 ml. per second from the aortic root to a Gilford densitometer through a sampling dead space of 1 0 ml The densitometer was modified so that the 90 per cent response time of the system was shortened to 0 23 to 0 30 sec To assure the avoidance of dye-curve distortion due to catheter sampling a figure of merit *[18] was calculated for each curve and when a value of 2 0 was exceeded because of tachycardia the measurement was rejected For each curve concentration was plotted semilogarithmically as a function of stroke number Except for the initial one or two beats on some curves concentrations uniformly fell on a single slope of exponential decay From this slope the ejection fraction (ratio of SV to EDV) was calculated as 1 (C_{N+1}/C_N) where C_N is the concentration on any beat C_{N+1} is the concentration on the succeeding beat and the concentration ratio (C_{N+1}/C_N) is obtained as the kth root of 0 1 where k is the number of beats required for a one decade fall in concentration Two to four measurements of ejection fraction were obtained for each stage of the study and EDV calculated as the ratio of mean SV to mean ejection fraction LV end systolic volume was obtained by subtracting SV from EDV Dye calibration was performed by an integrated sampling technique[18]

Dye curves pressures LV MRPR integrated LV pressure time and ECG were recorded on an Electronics for Medicine DR-8 Recorder Following hemodynamic measurements with the final angiotensin infusion used the drug was continued while LV angiograms were performed in 4 dogs of Group A and 2 of Group B No mitral regurgitation was evident. At the completion of the study all dogs were sacrificed by rapid intravenous KCl injections The hearts of the tricular KCl injections The hearts of the normal controls were examined to assure the absence of cardiac pathology In the

*Figure of merit (number of beats occurring during the time necessary to clear sampling system) = heart rate × dead space/sampling rate.

infarct groups the great vessels atria, and uninvolved right ventricle were removed from the left ventricle and septum. The remainder of the heart was then weighed before and after excision of the grossly infarcted area and the percentage of infected ventricle calculated

Various estimates of left ventricular function and contractility were calculated from the measured data before and following afterload tests with angiotensin LV stroke work (SW) in gram meters was calculated from the formula

$$SW = \frac{SV \times (LVS - LVEDP) \times 1\ 36}{100}$$

where SV is the stroke volume in milliliters LVS is the mean LV systolic pressure during ejection in millimeters of Hg LVEDP is the LV end-diastolic pressure in millimeters of Hg and 1.36 is the mercury correction factor Stroke power (SP) in gram meters per second was calculated by dividing SW by the average SEP over one respiratory cycle Mean rate of ejection (MRE) in milliliters per second[18] was calculated by dividing stroke volume by SEP

The radius of the ventricle was calculated from measured end-diastolic volume on the assumption of a spherical shape and the circumferential fiber length was calculated as $2\pi r$ Mean rate of circumferential fiber shortening (MRFS) was calculated by subtracting end-systolic from end-diastolic circumferential fiber length and dividing by SEP

Contractility was evaluated by an index expressing the end isovolumetric force velocity relationship corrected for differences in initial myocardial fiber length[11] This is expressed by the formula

$$\text{Index of Contractility} = \frac{MRIP\ \ MIP}{2\pi r}$$

where MIP is the maximal isovolumetric pressure (that pressure just before aortic valve opening) in millimeters of Hg and $2\pi r$ is the end-diastolic circumferential fiber length (EDFL)

Student's t test for unpaired data was used for the evaluation of statistical dif

ferences among the three groups. The t test for paired data was used to evaluate responses to angiotensin within each group Only initial resting data, before any angiotensin administration were used in comparing resting values among the three groups.

Results

Resting studies There were no significant differences between the normal dogs and the infarct groups in either weight (Normal 18.8 ± 1.0* Kg Group A 18 6 ± 1.8 Kg Group B 17 6 ± 0 9 Kg) or hematocrit (Normal 39 ± 2 per cent Group A 41 ± 2 per cent Group B 37 ± 1 per cent) Regardless of the arterial branch used for the induction of thrombus and infarction negligible amounts of right ventricle were involved and the percentage of left ventricle involved was similar between the two infarct groups (A 11 ± 2 per cent B 11 ± 1 per cent)

The only significant difference observed between the normal and infarct dogs among the variables measured directly at rest was the elevation of LVEDP among the latter (Tables I and II) In several cases this was accentuated by the presence of a large atrial impact wave (Fig 1) imposed upon the LV pressure pulse (Group A Dog 5 Group B Dogs 6 8 and 10) The elevated LVEDP was not accompanied by other findings which might indicate LV failure (e g elevated end-diastolic volume low cardiac output, stroke volume, or ejection fraction) The presence of an elevated LVEDP with normal LV end diastolic volume in the infarct dogs suggests decreased LV compliance. There were no significant differences between the normal and infarct dogs in other pressure measurements, cardiac index stroke work, maximal rate of LV pressure rise index of contractility or tension time index. Several variables characterizing LV ejection rate (stroke power mean rate of ejection and mean rate of circumferential fiber shortening) were reduced among the infarct dogs, the differences from normal becoming statistically significant by 6 to 8 weeks. There were no significant differences found between the early and late scar formation groups.

Afterloading with angiotensin During angiotensin infusion heart rate did not change significantly in any group and the aortic diastolic and mean pressures at each level studied were not significantly different among the three groups.

The responses of the normal and infarcted LV to augmented afterloading with angiotensin are indicated in Table III The normal group's response to the two afterload levels included significant rises ($p < 0.05$) in LVEDP (AII) EDV (AI AII) end-diastolic circumferential fiber length (AI AII) stroke work (AII) stroke power (AI AII) and tension time index (AII) and significant decreases in ejection fraction (AI) systolic ejection period (AI) mean rate of circumferential fiber shortening (AII) and index of contractility (AI AII) There were statistically insignificant increases in cardiac index and mean rate of ejection and there was no change in maximal rate of LV pressure rise Among both infarct groups no significant change in systolic ejection period or mean rate of circumferential fiber shortening was found with angiotensin. Aside from this the early scar formation group (A) response was similar to that of the normal group Group B

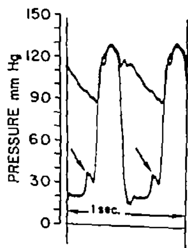


Fig 1 Superimposed LV and aortic pressures in Dog 8, Group B. Note prominent atrial impact waves on LV pressure pulse (arrows) with LVEDP of 32 mm Hg

*S.E. of the mean.

Table I Resting hemodynamics Dogs 3 to 4 weeks after myocardial infarction (Group A) and

Dog	HR (beats/min)	Ao_d (mm Hg)	$\overline{Ao}$ (mm Hg)	LVEDP (mm Hg)	CO (L./min)	CI (ml/Kg/min)	SV (ml.)	EDV (ml./Kg)
1 (ADA-8) 19 0 Kg	180	137	154	10	3 04	160	17	4 3
2 (LCA-7) 16 3 Kg	105	110	133	8	2 06	125	20	5 4
3 (ADA-10) 16 5 Kg	62	108	130	14	0 99	60	16	2 6
4 (ADA-7) 14 4 Kg	120	81	96	8	1 78	123	15	3 0
5 (ADA-22) 29 3 Kg	90	122	141	36§	1 82	62	20	2 4
6 (ADA-9) 18 1 Kg	102	96	114	12	1 69	93	17	3 4
7 (LCA-12) 15 9 Kg	140	89	108	6	1 70	107	12	2 4
Mean	114	106	125	13	1 87	104	17	3 4
±S E.M	±13	±7	±7	±4	±0 21	±13	±1	± 01
Normals†								
Range	67–155	68 127	76–155	0–9	1 61–3 50	75–220	11 37	2 3–5 0
Mean	115	102	117	5	2 30	127	21	3 6
±S.E.M	±9	±5	±7	±1	±0 19	±14	±2	±0 3
P values‡	NS	NS	NS	<0 05	NS	NS	NS	NS

Abbreviations HR = heart rat Ao = aorti diastolic (maximal isovolumetric) pressure; $\overline{Ao}$ = mean aortic pressure LVEDP left ve
E.F = ejection fraction EDFL = end-diastolic circumferential fiber length SW = stroke ork SP = st oke power; SEP = systol
sure rise I C. = index of contractility TTI = tension time index ADA = anterior descending branch lef coronary artery LCA left
Initials in parentheses indicate artery occluded followed by numeral indicating percentage of left ventricle infarcted.
†Ten dogs.
‡P values >0.1 listed as not significant (NS)
§Large atrial impact w superimposed on LV pressure pulse

however showed statistically significant increases in cardiac index at both pressor levels with angiotensin as well as an increase in mean rate of ejection (AII) and maximal rate of LV pressure rise (AI)

In general comparison of normal and infarct groups revealed no evidence of subnormal response to augmented after loading by angiotensin infusion during either the early or late stages of healing The differences observed at rest in LV ejection rate functions between normal and Group B dogs were less marked during angiotensin infusion and no new evidences of LV dysfunction were provoked by the increased afterloading in this late healing stage Moreover except for a significant difference in stroke power between the normal and Group A dogs, not observed at rest but elicited by the higher level of angiotensin infusion increased afterloading did not provoke or unmask any evidence of functional abnormalities not evident at rest in the early stage of scar formation

The three groups were also compared by plotting individual and mean values for stroke work (SW) against LVEDP and end-diastolic circumferential fiber length (EDFL) (Figs 2 to 4) The graphs for SW plotted against LVEDP for individual dogs in the three groups (Fig 2) demonstrate a shift down and to the right among the infarct dogs which might be interpreted as an indication of diminished LV function However when SW is plotted against EDFL (Fig 3) no differences are apparent Mean values for SW plotted against LVEDP (Fig 4) indicate more clearly a depressed function curve for the infarct dogs but when EDFL is plotted along the abscissa the three groups are indistinguishable

Discussion

Karsner and Dwyer examined the myocardium of dogs at various intervals fol

...terminals

EF	EDFL (cm.)	SW (gm M.)	SP (gm M./sec.)	SEP (msec.)	MRE (ml./sec.)	MRFS (cm./sec.)	LV MRPR (mm. Hg/sec.)	IC	TTI (mm. Hg/sec.)
.21	16 8	34 6	310	112	152	13 4	2820	1 24	13 3
.23	17 3	35 9	231	156	128	9 7	2890	1 52	21 9
.37	13 4	27 8	134	204	78	10 0	2280	1 58	28 9
.34	13 7	19 3	127	153	99	11 2	1660	1 49	15 5
.28	16 1	30 4	156	194	103	8 8	2600	1 32	28 8
.28	15 3	28 7	147	196	87	7 7	2455	1 67	26 6
.32	13 1	18 2	141	129	93	12 4	3300	2 84	15 1
.29	15 1	27 8	178	163	106	10 4	2572	1 67	22 1
±0 2	±0 6	±2 4	±24	±13	±9	±0 7	±182	±0 18	±2 1
.19–.44	13 1 17 1	11.5–64 5	94–394	112 210	85–204	8.8–23.3	1170–3040	0.85–1 76	9 6–27.8
.31	13 6	36 6	236	154	138	12 7	2234	1 40	19 8
.02	±0 5	±4 8	±30	±8	±14	1 4	±188	±0 10	±1 6
NS	NS	NS	NS	NS	=0 1	NS	NS	NS	NS

...stolic end-diastolic pressure; CO = cardiac output; CI = cardiac index; SV = stroke volume; EDV = left ventricular end-diastolic volume; ...ection period; MRE = mean rate of ejection; MRFS = mean rate of circumferential fiber shortening; MRPR = maximal rise of pressure; ...ventricular branch.

lowing ligation of the anterior descending branch of the left coronary artery. After 18 days a well-defined scar was apparent grossly although microscopically necrotic muscle and leukocytic infiltration were still interspersed with the connective tissue. The next stage studied was at 61 days and revealed condensation of the connective tissue and disappearance of the leukocytes. In studying human infarcts, Mallory and associates found collagen appearing at 3 to 4 weeks and essential healing of the infarcts at 2 months. Thus the infarcts of the Group A dogs (3 to 4 weeks) in the present study represent the early scar formation stage while the Group B dogs (6 to 8 weeks) represent the late stage of scar formation.

Studies of acute myocardial infarction in dogs have demonstrated transient falls in cardiac output and systolic pressure which then returned to normal, a decrease in LV MRPR[11,20] and either a rise[20] or no change[4] in LVEDP. In a closed-chest study performed 3 to 4 days after ligation Hood and associates[7] found an increase in LVEDP but no significant differences in aortic pressure, heart rate, cardiac index or MRPR in comparison with a group of sham-operated dogs. Stroke index was reduced only in dogs with greater than 20 per cent of the LV involved by infarction.

In the present study an elevation of LVEDP was also the most striking feature but, in the absence of other findings consistent with heart failure, must be regarded as reflecting altered ventricular compliance as has been demonstrated in various disease states.[22] The prominent atrial "kick" wave noted in several instances may indicate an adjustment of atrial contraction in an attempt to maintain normal end-diastolic volume and thus stroke volume in accordance with the Frank-Starling principle.[24] The limitations to interpreting LVEDP as an indication of end-diastolic volume are well recognized[25] and studies in man have uniformly shown poor correla-

Table II Resting hemodynamics Dogs 6 to 8 weeks after myocardial infarction (Group B) a

Dog	HR (beats/min.)	Aes (mm. Hg)	$\overline{Ao}$ (mm Hg)	LVEDP (mm Hg)	CO (L./min.)	CI (ml./Kg/min.)	SI (ml.)	EDV (ml./Kg
1 (LCA-8) 18.1 Kg	140	132	147	8	2.99	165	21	3.2
2 (LCA-8) 18.6 Kg	88	89	102	6	1.32	71	15	1.9
3 (ADA-15) 13.6 Kg	131	100	109	8	3.44	253	26	[illegible]
4 (ADA-12) 22.4 Kg	150	135	150	10	2.20	98	15	2.1
5 (ADA-8) 22.7 Kg	118	104	131	13	1.98	87	17	2.8
6 (LCA-10) 15.9 Kg	100	100	125	21§	2.25	141	23	3.4
7 (ADA-10) 16.3 Kg	175	118	136	9	2.62	160	16	4.1
8 (ADA-11) 17.3 Kg	100	90	110	32§	1.52	88	15	4.7
9 (ADA-15) 13.6 Kg	130	93	109	5	1.64	121	13	4.4
10 (ADA-14) 13.6 Kg	55	73	102	22§	1.14	84	21	2.3
11 (ADA-12) 21.6 Kg	133	88	106	17	3.26	151	24	—
12 (ADA-5) 17.3 Kg	118	92	100	5	1.38	80	12	2.9
Mean	120	101	119	13	2.14	125	18	3.8
±S.E.M	±9	±5	±5	±2	±0.22	±15	±1	±0.5
Normals†								
Range	67–155	68–1 7	76–155	0–9	1.61–3.50	75–220	11–37	2.3–5.0
Mean	115	102	117	5	2.30	127	21	3.6
±S.E.M	±9	±5	±7	±1	±0.19	±14	±2	±0.3
P values‡	NS	NS	NS	<0.01	NS	NS	NS	NS

Abbreviations as in Table I.
Initials in parentheses indicate artery occluded, followed by numeral indicating percentage of left ventricle infarcted
†Ten normal dogs.
‡P values >0.1 listed as not significant (NS)
§Large atrial impact wave superimposed on LV pressure pulse.

tion between the two regardless of whether volume was measured by angiographic[26] thermodilution[27] or dye dilution[17] techniques. It is therefore not surprising that similar ventricular volumes were found among the three groups of dogs despite the differences in LVEDP The importance of fiber length rather than resting tension or end-diastolic pressure was emphasized by Starling and his co-workers[5] in formulating the law of the heart In the present study the conflicting results obtained when fiber length rather than LVEDP was plotted against stroke work indicate that use of end-diastolic pressure in this instance is misleading and that in terms of the Frank Starling aspect of myocardial function the infarcted ventricles were not impaired

Ventricular performance can also be characterized in terms of the force velocity relations studied in skeletal muscle by Hill[29] and recently shown to be applicable to heart papillary muscle[30,31] to the intact hearts of anesthetized animals[32,33] and to the left ventricle of man[33,34] In the present study evaluation of the relationship between instantaneous values for velocity force and length using the index of Frank and Levinson[22] indicates that left ventricular contractility is normal in both early and late stages of healing after myocardial infarction Previous studies[35,36] have shown that myocardial fiber shorten-

...ormals

EF	EDFL (cm.)	SW (gm M)	SP (gm M/sec)	SEP (msec.)	MRE (ml/sec.)	MRFS (cm./sec)	LV MRPR (mm Hg/sec)	I C	TTI (mm. Hg/sec)
.22	17.8	43.2	283	153	138	9.8	2720	1.16	24.4
42	12.9	20.4	92	220	69	10.0	1820	1.59	23.5
.23	18.3	37.4	220	169	154	10.1	2320	1.27	19.3
31	14.1	30.0	203	148	101	10.8	3560	1.88	23.4
27	15.5	28.4	140	204	83	7.9	2400	1.49	27.6
42	14.7	34.4	168	204	110	11.5	1960	1.33	26.6
19	16.2	30.6	243	126	127	10.3	2915	1.52	18.9
39	13.2	17.9	94	190	79	10.0	2660	2.24	22.9
20	15.6	19.6	128	154	85	7.2	2010	1.39	17.7
30	14.8	28.2	112	251	84	8.0	2040	1.88	30.7
—	—	33.2	177	188	127	—	3220	—	22.4
24	14.3	18.4	116	158	76	7.6	2485	1.88	20.7
30 03	15.2 ±0.5	28.5 ±2.2	165 ±18	180 ±10	103 ±8	9.4 ±0.4	2509 ±154	1.60 ±0.10	23.2 ±1.1
.19–.44 31 02 NS	13.1–17.1 15.6 ±0.5 NS	11.5–64.5 36.6 ±4.8 NS	94–394 236 ±30 <0.05	112–210 154 ±8 <0.10	85–204 138 ±14 <0.05	8.8–23.3 12.7 ±1.4 <0.05	1170–5040 2234 ±188 NS	0.85–1.76 1.40 ±0.10 NS	9.6–27.8 19.8 ±1.6 <0.10

ing in the intact left ventricle of normal dogs is determined by the levels of three factors preload afterload, and contractility. Since these did not differ in the normal and infarct animals in the present study the abnormalities in rate functions during ejection imply the operation in the infarcted ventricle of a *fourth factor* which results in retarded contraction despite normal contractility. It may be that the presence of a scar in the otherwise normal left ventricular wall prevents the translation of apparently unimpaired pre-ejection event (contractile element shortening) into normal ejection performance (i.e. rate of ejection). It is significant that these abnormalities in velocity of ejection were similar in the two groups of infarct dogs, indicating that no improvement in LV function occurs between early and late scar formation.

The failure to further differentiate the infarct dogs from the normals in this study by afterloading with angiotensin is of interest. Although angiotensin ordinarily has only negligible inotropic actions in the intact animal it may have more pronounced inotropic effects in the damaged or abnormal heart.[36,37] This may have been manifested in the present study by the significant increases in cardiac output seen in the Group B dogs following angiotensin and the tendency toward an increase in mean rate of ejection and fiber shortening

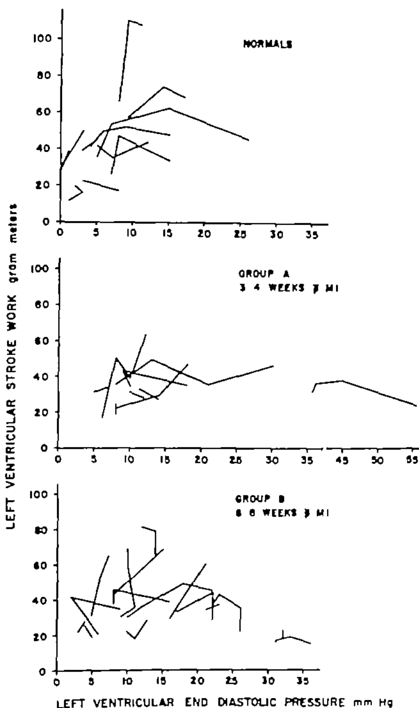


Fig 2 Individual LV function curves, with stroke work plotted against LV end-diastolic pressure. Curves in infarct groups appear shifted down and to the right

while these were unchanged or fell slightly in the normal dogs (Table III) It is also noteworthy that Ross and Braunwald[19] used angiotensin afterloading to detect abnormalities of ventricular function in patients more likely to have diffuse left ventricular involvement because of the underlying pathology (rheumatic heart disease, cardiomyopathies) while in the dog model studied a rather well-defined scar had been produced within an otherwise normal left ventricle

Although study of myocardial function following MI in this experimental model offers obvious advantages in terms of control extent of investigative procedures used and accurate physiologic pathologic correlation the relevance of these findings to naturally occurring MI in man must be considered Certainly the status of the

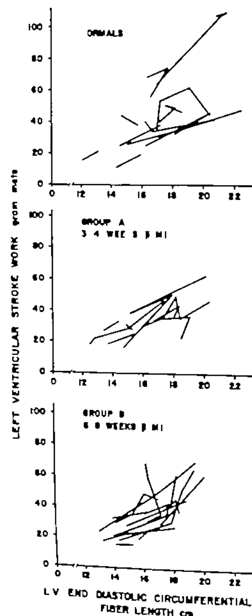


Fig 3 Ind idual LV function curves with stroke ork plotted against end-diastolic circumferential fiber length. Curves for all three groups appear similar

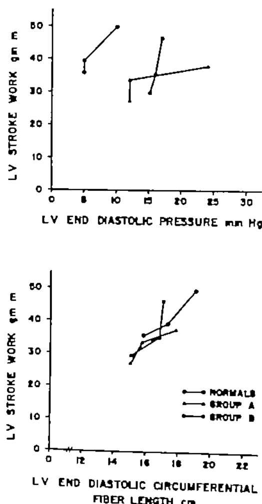


Fig 4 Mean values for stroke ork plotted against LV end-diastolic pressure (upper panel) and stroke work plotted against LV end-diastolic circumferential fiber length (lower panel) for the three groups of dogs t rest and t the tw afterloading levels. LV f nction curves for the infarct groups appear depressed in the upper panel but not in the lower panel.

coronary arteries and the degree of myocardial involvement in clinical MI can be much more variable than encountered here in the dog. Hemodynamic studies in man ea ly after acute infarction have demon strated extremely variable findings[38,39] and have excluded analyses of left ventricular function Among patients with healed myocardial infarction however some simi larities with the current study have been found Elevations in LVEDP are a frequent finding in the absence of other indi cations of heart failure[40] Increased a wave amplitude in precordial low frequency recordings has been noted in association with elevated LVEDP[41,42] and mean ejection rate has been found to be reduced[43] These similarities support the validity of the experimental model used

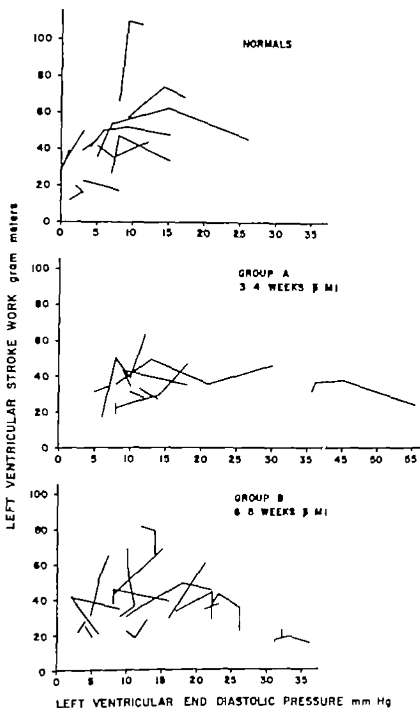


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Although study of myocardial function following MI in this experimental model offers obvious advantages in terms of control extent of investigative procedures used and accurate physiologic pathologic correlation the relevance of these findings to naturally occurring MI in man must be considered Certainly the status of the

SP (pm. M./sec)	*SEP* (msec.)	*MRE* (ml./sec)	*MRFS* (cm./sec)	*LV MRPR* (mm. Hg/sec.)	*IC*	*TTI* (mm. Hg/sec.)
234	157	139	12 8	2100	1 29	20 3
±27	±10	±14	±1 4	±193	± 10	±1 7
329	142	171	12 0	2204	1 10	20 8
±46	±11	±24	±1 1	±235	± 12	±1 7
224	152	133	10 7	2291	1 39	19 5
26	±5	±12	±1 0	±198	± 08	±1 7
310	154	148	9 0	2179	0 91	25 1
±25	±7	±14	±1 1	±172	± 10	±1 9
165	159	98	10 0	2456	1 54	21 3
±21	±10	±9	±0 6	±172	± 10	±1 8
218	163	118	10 6	2541	1 29	24 5
±27	±11	±12	±0 9	±176	± 11	±2 0
196	154	113	9 9	2648	1 43	21 5
±23	±9	±9	±0 6	±160	± 09	±1 7
236	164	120	7 9	2529	0 94	27 7
±21	±11	±9	±0 9	±176	± 05	±2 3
168	181	111	9 4	2383	1 53	23 0
±17	±9	±11	±0 5	±114	±0 7	±1 2
208	172	122	9 1	2526	1 33	24 1
±22	±11	±12	±0 5	±122	± 06	±1 4
166	184	107	9 1	2503	1 65	23 5
±17	±10	±10	±0 4	±138	± 06	±1 1
266	176	134	8 6	2670	1 15	28 2
±28	±11	±13	±0 9	±153	± 05	±1 7
<0 01	<0 05	<0 1	NS	NS	<0 02	NS
<0 01	NS	<0 1	<0 05	NS	<0 01	<0 001
<0 02	NS	<0 1	NS	NS	<0 01	<0 1
<0 1	NS	NS	NS	NS	<0 01	<0 05
<0 01	<0 1	<0 1	NS	<0 05	<0 05	NS
<0 001	NS	<0 05	NS	<0 1	<0 001	<0 01
<0 1	NS	<0 1	NS	NS	NS	NS
<0 02	<0 1	<0 1	<0 05	NS	<0 1	NS
<0 05	NS	NS	NS	NS	NS	NS
NS	<0 1	NS	NS	<0 1	NS	NS

In above control, AII angiotensin infusion causing to 40 mm. Hg rise in aortic diastolic pressure. Other abbreviations as in Table I.

In both the early and late stages of scar formation the infarcted ventricles had normal end-diastolic volumes and normal isovolumetric velocity-force length relationships but elevated resting end-diastolic pressures. LV ejection-rate functions (stroke power mean rate of ejection and mean rate of circumferential fiber shortening) were reduced after MI the differences becoming statistically significant by 6 to 8 weeks. There were no significant differences found between the two infarct groups. With augmented afterloading LV function after MI appeared depressed when stroke work was plotted against LV end-diastolic pressure but not when plotted against end-diastolic circumference. Thus, although its length tension (Frank Starling) characteristics and isovolumetric velocity-force length (contractility) relationships were

Table III Effect of afterloading with angiotensin infusion

Group	LVEDP (mm Hg)	CI (ml/Kg)	EDV (ml/Kg)	E.F	EDFL (cm.)	SIT (gm M)
Normals						
CI (10) d	4	119	3 6	31	15 8	37 4
±S.E.M	±1	±14	±0 3	± 02	±0 5	±5 2
AI	5	132	4 7	26	17 3	39 1
	±1	±14	±0 5	± 02	±0 9	±7 8
CII (8)	4	110	4 0	25	16 4	34 5
	±1	±10	± 3	± 02	±0 3	±4 4
AII	10	126	6 4	22	19 0	49 8
	±2	±15	±0 8	± 03	±0 7	±15 5
Group 1						
CI (9) d	12	102	2 9	29	14 4	25 0
±S.E.M	±3	±11	±0 3	± 01	±0 5	±2 1
AI	12	121	3 9	29	15 7	33 7
	±3	±13	±0 5	± 02	±0 6	±2 7
CII (8)	15	109	3 7	25	15 8	29 2
	±4	±12	±0 5	± 01	±0 6	±2 5
AII	24	117	5 0	22	17 8	37 6
	±6	±14	±0 4	± 03	±0 4	±2 7
Group B						
CI (14) d	15	132	4 1	30	15 3	29 7
±S.E.M	±2	±14	±0 5	± 02	±0 4	±3 3
AI	16	149	5 3	24	16 8	35 0
	±2	±14	±0 4	± 01	±0 4	±3 9
CII (16)	14	118	3 7	30	15 0	29 0
	±2	±13	±0 5	± 02	±0 4	±2 9
AII	17	149	5 3	26	17 0	45 8
	±2	±14	±0 6	± 02	±0 5	±4 7
P values†						
A CI vs. AI	NS	NS	<0 05	<0 02	<0 05	<0 1
CII vs. AII	<0 01	NS	<0 02	<0 10	<0 01	<0 01
A CI vs. AI	NS	=0 05	<0 05	NS	<0 02	<0 05
CII vs. AII	<0 01	NS	<0 01	NS	<0 02	<0 1
B CI vs. AI	<0 1	<0 05	<0 05	<0 02	<0 001	<0 01
CII vs. AII	<0 05	<0 05	<0 02	NS	=0 01	<0 01
AI N vs. A	<0 05	NS	NS	NS	NS	NS
N vs. B	<0 01	NS	NS	NS	NS	NS
AII N vs. A	=0 05	NS	NS	NS	NS	NS
N vs. B	=0 05	NS	NS	NS	<0 05	NS

Abbreviations: CI, CII = control values before AI and AII infusions AI = angiotensin infusion bringing aortic diastolic pressure 10 to 20 m

Number in parenthesis indicates number of measurements.

†P values >0.10 listed as not significant (NS)

in studying various aspects of LV function as might be encountered in naturally occurring myocardial infarction in man

Summary

To evaluate changes in left ventricular (LV) function after myocardial infarction (MI) anesthetized closed-chest dogs were studied following survival from acute non massive MI induced by thrombus formed on a catheter electrode in either branch of the left main coronary artery Seven dogs were studied 3 to 4 weeks after MI (early scar formation) and 12 dogs 6 to 8 weeks after MI (late scar formation) Ten normal dogs with heart rates and aortic pressures similar to the MI groups served as controls LV function was evaluated at rest and during afterloading with angiotensin

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not altered the healing infarcted ventricle exhibited reduced velocity of shortening during ejection and increased LV end diastolic pressure which in the absence of evidence of cardiac decompensation proba bly reflects a reduced compliance

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others with 0.35 to 0.50 ml. daily of water in the same manner. Two hundred sixty other animals received no pretreatment. All 300 animals were then given subcutaneous injections of 25 mg. per kilogram of the synthetic beta adrenergic stimulating agent, 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol (isoproterenol)* for 2 consecutive days by the method of Rona and co-workers.[6] This dose of isoproterenol was selected after preliminary experiments revealed its ability to regularly produce extensive myocardial necroses and still have a high survival rate (70 to 100 per cent).

The 201 surviving animals who received no pretreatment were randomly assigned to 3 groups as follows: (1) a control group of 69 rats received no treatment; (2) a control group of 67 rats received daily subcutaneous injections of 3.5 to 0.5 ml. of distilled water; (3) a group of 65 rats received daily subcutaneous injections of 3.5 to 0.5 ml. of 90 per cent DMSO (approximately 1 to 2 mg. per kilogram which is in the anti-inflammatory dose range). The 26 surviving animals who received pretreatment with DMSO or water were continued on the same treatment following the two injections of isoproterenol. Animals from each group were put to death with ether 2, 14, and 30 days after the second injection of isoproterenol. The hearts were removed and fixed in 10 per cent formalin. The atria were excised and the ventricles were divided into 3 pieces by sectioning through the apical, middle, and basilar portions. Five transverse serial histologic sections were then made from each of the 3 pieces of ventricle and stained with hematoxylin and eosin and Masson's trichrome stains. The histologic slides were coded so that their origins were unknown to the grading observer. The severity and extent of the myocardial lesions were then quantitatively evaluated by the method of Gal and co-workers.[24] This method comprises evaluation of the three most characteristic and prominent features of isoproterenol-induced lesions, namely, fiber necrosis, stromal changes, and cellular infiltration. Lesions containing more than 20 infiltrating cells are defined as "greater"

and those consisting of fewer than 20 infiltrating cells "smaller." The severity and extent of the lesions were scored according to the following criteria:

1. Necrosis of the myocardial fibers in a greater area 2.0 points
2. The same in a smaller area 1.0 point
3. Loosening of the interstitium in a greater area 1.0 point
4. The same in a smaller area 0.5 point
5. Great circumscribed cellular focus 1.0 point
6. Small circumscribed cellular focus 0.5 point

After examining each section, the numerical score was totaled to obtain a "myocarditis score" for each heart. Ventricular areas were then determined in square centimeters by planimetry and each "myocarditis score" was then divided by the area of the ventricle from which it was obtained to yield the "myocarditis index." The mean "myocarditis index" was then determined for each group at each of the 3 times the animals were sacrificed. Analysis of variance was used for statistical evaluation.

Results

Uniform focal and confluent infarct-like myocardial lesions similar to those described by other investigators[11,25] were found in all rats receiving subcutaneous injections of isoproterenol. Pretreatment with injections of DMSO or water failed to alter the mortality rate. The severity of the myocardial lesions in the pretreated animals was essentially the same as in the animals first receiving these treatments after isoproterenol administration. Thus the data obtained from the pretreated animals was pooled with that of the main DMSO and water treated groups. Fig. 1 shows typical myocardial lesions on the second day after isoproterenol administration. These lesions primarily involved the apex, papillary muscles, and intraventricular septa and were most marked in the subendocardial regions. The histological picture in all 3 groups at this time was characterized by swelling and necrosis of myocardial fibers, cellular infiltration

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The effects of dimethylsulfoxide (DMSO) on the healing of experimental myocardial necrosis

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Dimethylsulfoxide (DMSO) is an organic liquid obtained as a by product of the paper pulp industry. It possesses a broad spectrum of interesting physiochemical and pharmacological properties. These include broad solvent properties[1] the ability to protect cells and tissues from damage during freezing, thawing, and ionizing radiation,[2,3] the ability to rapidly traverse animal membranes and tissues including skin carrying other chemicals along with it[4-6] and potent anti-inflammatory properties.[7-9] Anti-inflammatory activities include the inhibition of inflammation and edema formation[7] mucopolysaccharide synthesis[8] granulation tissue development[7,8] and in vitro fibroblastic proliferation.[9] Clinically it has been shown to be of benefit in acute and chronic musculoskeletal injuries and inflammations[10-15] and in reversing the cutaneous manifestations of scleroderma, particularly the healing of ischemic ulcers of the fingertips.[16,17] It also may be of value in management of peripheral arteriosclerotic occlusive disease.[18] A possible use for DMSO in the treatment of cardiac disease was suggested by the above mentioned pharmacologic actions. In addition, Finney and associates[19] were successful in preventing myocardial infarction in pigs with ligated coronary arteries by pericardial infusions of DMSO-hydrogen peroxide solutions. The purpose of this study was to determine the effects of DMSO on the healing of isoproterenol induced infarctlike lesions in rats.

Methods and materials

Young male rats of the Walter Reed strain† weighing 250 to 300 grams (mean weight 271 grams) were used in these experiments. The animals were housed 2 to a cage in an air-conditioned room and fed commercial rat and mice biscuits. Twenty animals were pretreated for 7 days with daily subcutaneous injections of 0.35 to 0.50 ml. of 90 per cent DMSO‡ and 20

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†The principles of laboratory animal care as promulgated by the National Society for Medical Research were observed.
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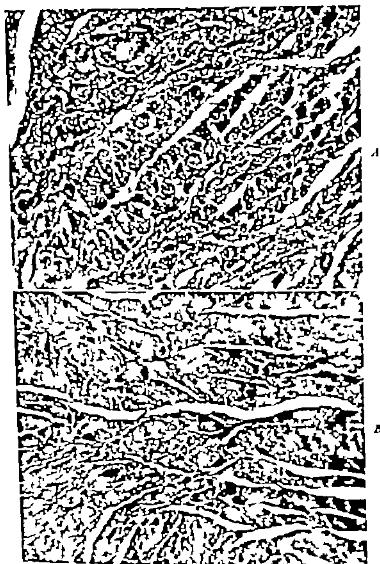


Fig. 2. Photomicrographs taken at the same magnification (×160) of the subendocardial portion of the myocardium of rats from the control group (*A*) and the DMSO-treated group (*B*) put to death three days after the second injection of isoproterenol. *A*, In the control group scattered vacuoles along with a moderate amount of fibrous connective tissue are still present between myocardial bundles, particularly in the top central portion. *B*, In the DMSO-treated animals the residual fibrosis is small in amount and only occasional vacuoles are noticed between myocardial bundles.

treated rats, respectively 30 days after induction of necrosis. It is evident that the DMSO treatment resulted in more complete healing and less residual fibrosis. The water treated group showed an intermediate amount of scar tissue.

The myocarditis indices rating the severity and extent of the histological lesions in the three groups during each of the time periods are seen in Table I. The indices for the DMSO- and water treated groups at both Days 2 and 30 were significantly less ($p < 0.01$) than the index for the untreated group. However at 14 days there were no statistically significant differences in the indices among the three groups. In all three groups, there were statistically significant decreases in the severity of the lesions with time ($p < 0.01$) as reflected by the indices.

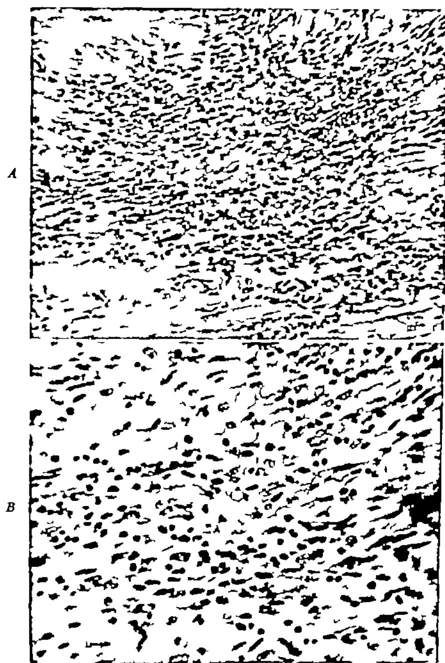


Fig 1 Photomicrographs of typical myocardial lesion in rat from the control group put to death two day after the second injection of isoproterenol. *A* Massive swelling and necrosis of myocardial fibers along with vacuolization and cellular infiltration are present throughout the myocardium. (×160) *B* A typical zone of necrosis exhibits hyalinization of muscle fibers loss of myocardial bundles cellular infiltrates comprising leukocytes mononuclear cells, and fibroblasts, capillary dilatation interstitial edema, and the appearance of small clear vacuoles. (×400)

with leukocytes mononuclear cells, and fibroblasts and capillary dilatation and interstitial edema Ventricular aneurysms were seen in 20 per cent of animals from the two control groups but not in the DMSO-treated group Fourteen days after injection of necrosis progression of the healing process was evident. The DMSO treated group at this time showed fewer hyalinized necrotic muscle fibers than did the two control groups. The lesions in the DMSO treated group consisted predominantly of stromal alterations. The untreated group at this time showed a deeper blue staining of the fibrous connective stroma with Masson's trichrome stains than did the DMSO or water treated groups suggesting a greater deposition of mucopolysaccharides Fig 2 shows typical lesions in the untreated and DMSO

this study it would appear worthwhile to investigate further the effects of DMSO on healing of cardiac lesions.

Summary

DMSO treatment of rats with isoproterenol-induced myocardial infarctlike necrosis results in less myocardial fiber necrosis, absence of ventricular aneurysms and cardiac rupture, delayed healing and a smaller residual area of myocardial fibrosis.

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Table I Effect of DMSO and water treatments on severity of myocardial lesions produced by isoproterenol

Treatment	Myocarditis indices (Score/cm ± S.E.M.) following second isoproterenol injection		
	2 days	14 days	30 days
None	62.4 ± 4.7	28.9 ± 3.6	27.7 ± 3.0
Water	41.3 ± 2.9	18.7 ± 2.3	17.0 ± 4.5
DMSO	36.7 ± 3.2	27.7 ± 4.8	12.4 ± 3.0*

Change in size of lesions between Days 2 and 30 statistically significant ($p < 0.01$) for all three groups.

*P value < 0.01 when compared with control group by analysis of variance

Despite the qualitative differences in the lesions described above there was no significant difference between the myocarditis indices of the DMSO- and water treated groups at any time A difference in the healing pattern was noted in the DMSO group as compared to the other two groups The severity of the lesions in the untreated and water treated groups decreased rapidly between Days 2 and 14 and then remained essentially unchanged up to Day 30 In the DMSO group the lesions showed a much smaller decrease in severity between Days 2 and 14 than the other 2 groups and the major regression in severity of the lesions occurred between Days 14 and 30

Discussion

Although the pathogenesis of the isoproterenol induced myocardial necrosis is still not completely settled the results of pharmacological and other experimental studies and the gross and histological features of the myocardial lesions are consistent with an ischemic pathogenesis [22,24] This experimental model has been widely used to test drugs for possible value in coronary insufficiency by seeing if rats pretreated with them have less severe myocardial necrosis following isoproterenol administration [22,23,24] Recently it has also been used to evaluate the effect of drugs on the healing of myocardial necrosis.[25] Pharmacologic and other factors which modify isoproterenol cardiac necrosis have previously been reviewed [22,24,26]

In this study daily subcutaneous injections of both water and DMSO significantly reduced the severity of isoproterenol induced necrosis in rats. The stress associated with the daily injections probably played a role in the reduction of the extent of the lesions. Selye[27] previously noted that stress can inhibit the induction of cardiomyopathies by otherwise effective doses of cardiotoxic drugs. In using this experimental model this stress factor should be controlled

DMSO administration appeared to favorably modify the character of the myocardial lesions from those seen in the untreated and water treated groups. The lesions in the DMSO treated rats consisted primarily of stromal alterations with less myocardial fiber necrosis than the other two groups. Ventricular aneurysms and cardiac ruptures, occasionally seen after isoproterenol induced necrosis, were not found in the DMSO-treated group probably as a result of reduced fiber necrosis. Cardiac muscle when irreversibly damaged cannot regenerate thus DMSO must have prevented the death of injured myocardial fibers Perhaps the mechanism of this beneficial effect was an alteration in tissue permeability so as to increase oxygenation and nutrition of the ischemic myocardium A similar mechanism was proposed to explain how DMSO protected pigs with ligated coronary arteries from myocardial infarctions when infused with hydrogen peroxide into the pericardium [18] and to account for the improvement noted in patients with arteriosclerosis obliterans when treated with DMSO [19] A shift in myocardial electrolytes with an outward flow of potassium is believed to play an additive role in the production of myocardial necrosis.[22] Perhaps part of the protective effect of DMSO in isoproterenol induced necrosis is due to a reversal of this shift

The delay in healing of the lesions in the DMSO treated group probably resulted from an inhibition of synthesis of mucopolysaccharides and collagen fibers. This has been previously noted with DMSO and other antiphlogistics [8] The end result of the DMSO treatment on the myocardial necrosis was a reduced area of residual myocardial fibrosis. From the results of

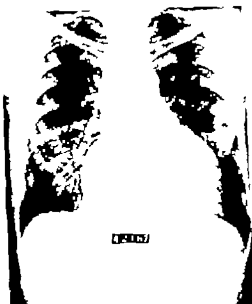


Fig. 1 This chest radiograph shows the appearance of the heart shadow on the day oral prednisone was begun. It is typical of several made during the ten days prior to corticoid therapy. The markedly enlarged cardiac silhouette is compatible with pericardial effusion.

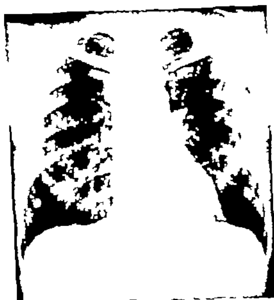


Fig. 3 This chest radiograph made in April, 1968, at the time of cardiac catheterization demonstrates that the heart size is now only slightly increased above normal.



Fig. 2 This chest radiograph made after six days of oral prednisone demonstrates considerable reduction in the size of the cardiac silhouette.

friction rub appeared and persisted. H was admitted to the hospital on April 19 1967 because of persistent low grade fever exertional dyspnea, and marked increase in heart size on x-ray (Fig. 1). The blood pressure was 120/76 and 10 to 15 mm. inspiratory decline in the systolic level was noted. The neck eins were slightly distended as the patient reclined t 45 degrees, but their wave form was normal, and they appeared to collapse with inspiration. The pericardial rub persisted. The blood urea nitrogen was 31 mg. per cent, the creatinine 8.6 mg per cent, the hemoglobin 6.4 Gm. per cent, and the hematocrit 20 per cent. Subxiphoid pericardiocentesis yielded 100 c.c. of bloody fluid having hematocrit of 9 per cent appropriate cultures of the fluid for pyogenic bacteria, *Mycobacterium tuberculosis*, fungi, and common viruses were unrewarding. An intermediate strength purified protein deriv tiv skin test was negative. Prednisone, 60 mg per day by mouth, was begun April 29 and six days later the cardiac silhouette was considerably reduced in size (Fig. 2). Unfortunately it was necessary to stop the prednisone May 12 because the catabolic effects of the drug resulted in marked increments of the blood urea nitrogen between dialyses.

On May 26, he was readmitted after becoming hypotensive during dialysis. Volume expansion improved the circulatory status, however the venous pressure was then seen to be distinctly elevated and pulsus paradoxus (15 mm.) was present. Pericardiocentesis yielded 500 c.c. of grossly bloody fluid 60 mg. of methylprednisolone were injected into the pericardial cavity. Following this, evidences

Case reports

Chronic constrictive pericarditis following uremic hemopericardium

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Uremic pericarditis may no longer be regarded as merely an interesting finding in patients dying of renal failure. Quite a number of reports are now available to attest to the frequency with which uremic pericardial effusion results in cardiac tamponade even in patients maintained on chronic hemodialysis.[1-4] Furthermore, a thick fibrous densely adherent pericardial scar is an occasional autopsy finding in such patients.[4]

It may be anticipated that instances of chronic constrictive pericarditis will be found among the ever increasing number of patients whose lives are sustained by chronic hemodialysis and who have survived one or more episodes of uremic hemopericardium. To our knowledge two patients characterized as manifesting subacute constrictive pericarditis due to uremia have been reported.[5,6] In another pericardiectomy was required two months following septic uremic pericarditis.[7] It is our purpose to describe a patient who we believe is the first in whom chronic constrictive pericarditis was the documented sequel to uremia.

Case report

In 1946, a 26-year-old Caucasian man was hospitalized for three months because of hematuria. He was then well until 1963 when edema and proteinuria appeared.

In 1964, at the age of 44, he entered the Atlanta Veterans Administration Hospital for the first time because of generalized edema. At that time he was excreting as much as 14 Gm. of protein daily in his urine. Hypoalbuminemia and hypercholesterolemia completed the picture of the nephrotic syndrome. Membranous glomerulonephritis was diagnosed from tissue obtained by needle biopsy of the kidney. A brief course of adrenocorticosteroid therapy and diuretics produced some amelioration of the findings; however, during 1965 and 1966, he was hospitalized repeatedly because of progressive azotemia, acidosis, hyperkalemia, and anemia. On one occasion he complained of pleuritic precordial pain and a pericardial friction rub was transiently present.

After another trial of corticosteroid therapy produced no improvement in his persistent edema and azotemia, the patient began on a program of hemodialysis twice a week at the Atlanta Dialysis Center in January, 1967. Isoniazide was given along with the corticosteroid trial and was continued thereafter. The blood urea nitrogen was maintained below 50 mg. per cent; however, the patient remained anemic.

In March, 1967, precordial pleuritic pain which radiated to the back and shoulders appeared. A chest x-ray revealed no abnormalities. A pericardial

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Table I. Right heart catheterization

Pressures (mm. Hg)	*Values*
Right atrium	Mean 15 = 17 = 17
Right entricle	35/16
Pulmonary artery	35/16 mean 21
Pulmonary artery wedge	Mean 16 = 21 v = 22
Systemic artery	166/77 (11 mm. inspiratory fall of systolic pressure)
Cardiac index (Indocyanine green dy curv)	3 4 L. per min to per square meter

of tamponade ere no longer present and did not recur

During the ensuing six months, the clinical condition was stable No further evidence of pericarditis was detected The patient complained of a reduction in his exercise tolerance which his physicians attributed to his persistent anemia. Serial radiographs demonstrated progressive reduction in the cardiac silhouette to near normal size (Fig 3).

In December 1967 examination revealed blood pressure of 130/86 Inspiratory diminution of systolic arterial pressure amounted to 8 mm Hg The heart rate as 80. The patient was thin, pallid, and chronically ill. The jugular venous pulse, visible above the clavicles with the patient seated upright, exhibited deep and y troughs (Fig. 4) The apex impulse, located i the fourth left intercostal space inside the midclavicular line, consisted of diastolic outward movement and systolic retraction (Fig 5). A short ejection systolic murmur as heard t the lower left sternal border and, most significantly loud early diastolic sound typical of pericardial knock as heard over the apex and at the left sternal border

I April, 1968, cardiac catheterization provided findings consistent ith compressive cardiac disorder (Table I) Angiography and cineangiography with injection of contrast material in the right atrium demonstrated straightened, rigid trial all hich was abnormally thickened to 7 mm (Fig. 6)



Fig 6 A frame from the right atrial angiogram demonstrates the thickened right atrial wall. This extraluminal opaque band persisted in all frames. Cineangiography demonstrated immobility of the lateral margin of the contrast material and considerable reflux into the inferior vena cava.

Discussion

Although there are two previous reports of subacute constrictive pericarditis, the present patient is the first in whom the picture of a restrictive pericardial scar has followed uremic hemopericardium Spodick pointed out that there are no pathognomonic clinical or laboratory findings of chronic constrictive pericarditis, but he recognized that the diagnosis can accurately be made when a constellation of typical features are present. The diagnosis in the present case is based upon such a constellation—characteristic physical findings, corroborated by compatible hemodynamic and angiographic data.

The physical signs exhibited by this patient first directed attention to the diag

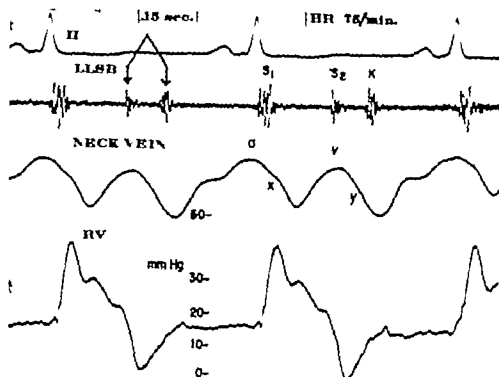


Fig 4 These recordings were made in April 1968 at the time of cardiac catheterization. The phonocardiogram demonstrates the pericardial knock (*K*) The prominent x and y troughs of the venous pulse are seen by the indirect neck vein recording The right ventricular pressure recording (*RV*) illustrates the early diastolic dip and high diastolic plateau characteristic of restrictive cardiac disorders. Time lines denote a one-second interval.

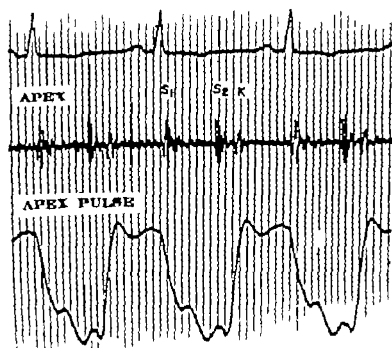


Fig 5 A recording of the apex impulse (apex cardiogram) along with Lead II of the electrocardiogram and the apex phonocardiogram reveals the systolic retraction of the apex. Intervals of 0.04 second are denoted by the time lines.

Summary

A case of chronic constrictive pericarditis following uremic pericarditis is reported.

Physicians caring for patients who have survived episodes of uremic pericarditis should be alert for the signs of a restrictive cardiac disorder.

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nosis. The systemic venous pressure was considerably raised as evidenced by jugular venous pulsations visible with the patient in the upright posture Brisk x and y troughs were detected Wood[8] called attention to such a pattern in certain patients with this disorder Systolic retraction of the apex as observed and recorded here, is seen frequently in constrictive pericarditis but may also be due to pericardial scarring of no hemodynamic consequence or to marked right ventricular hypertrophy[8] The auscultatory and phonocardiographic characteristics of the third heart sound were typical of pericardial knock[8] The duration of the interval between this sound and aortic closure has been thought to depend at least partially upon the level of inflow pressure A narrow 2 K interval seems to correlate with high filling pressures in a manner analogous to the 2-OS interval of mitral stenosis.[8] It can be seen that the 2 K interval is 0 15 sec in Fig 4 This recording was made at the time of cardiac catheterization one day after hemodialysis Fig 5 depicts a considerably shorter interval This recording was obtained several months prior to the catheterization and immediately prior to a dialysis. We suspect that reduction in blood volume by dialysis and thus inflow pressure accounts at least in part for the variation

The hemodynamic data obtained at cardiac catheterization support the clinical impression of a restrictive cardiac disorder Although the abnormalities of pressure and flow could have been produced by myocardial disease they are quite typical of constrictive pericarditis The near equality of the mean pressure in the right atrium and pulmonary artery wedge position is characteristic. A diastolic plateau typified the right atrial right ventricular and pulmonary artery pressure pulses. The right ventricular pressure dipped briskly in early diastole rising abnormally to a level greater than one third of the systolic pressure (Fig 4)

Angiography and cineangiography documented a thickened pericardium Furthermore, the lateral wall of the right atrium appeared straightened and immobile as described in constrictive pericarditis.[10,11]

... likely that chronic constrictive pericarditis is a sequela to uremic pericarditis in at least a few patients who survive for a period of time adequate to allow the formation of a dense scar The possibility that chronic dialysis is involved in some direct way with the pathogenesis of the pericardial problems of uremia is however worth considering Some investigators have felt that anticoagulation during hemodialysis may under proper circumstances, promote bleeding into the pericardium[2] Repeated bleeding of this nature might be important in the ultimate development of a restricting scar While considering reasons for the development of a constricting pericardial scar in this patient, one must not overlook the possibility that the intrapericardial adrenal steroids played a role in its development We feel it is unlikely that they played a significant role

The implications of restrictive pericardial disease in the conduct of dialysis have been noted by Hager[1] The ability of patients with cardiac compressive disorders to adapt to a reduction in cardiac filling pressure is compromised Accordingly care should be taken to assure that an injudicious reduction in blood volume is not incurred during dialysis. It is noteworthy that the patient reported here complains of significant weakness following dialysis during which a weight loss averaging 1 5 kilograms occurs He feels that he is strongest immediately prior to the procedure It is often necessary to administer agents to expand the vascular volume at the end of the procedure to achieve satisfactory arterial pressure and adequate blood flow through the A V shunt

The apparent reduction in the hemopericardium in this patient following adrenal steroid therapy was impressive. This was, however less striking than the response often attending this therapy in other forms of pericarditis. The increased protein catabolism associated with systemic administration of steroids may limit the use of these agents in uremic patients In this instance this effect was circumvented by direct instillation of methylprednisolone into the pericardial cavity Although the effect appeared salutary conclusions concerning the therapeutic efficacy of this maneuver must await additional experience

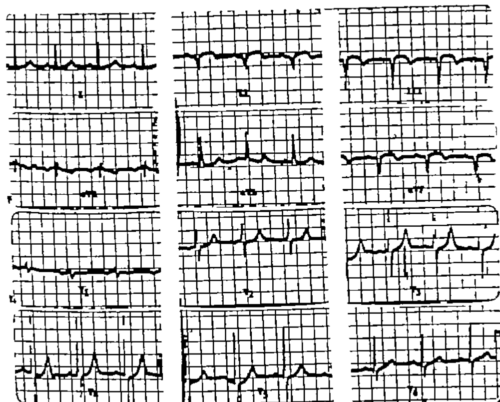


Fig. 1 Admission electrocardiogram revealing acute posterior myocardial infarction

ere instituted, with apparent subsidence of the conduction defect during that night However the following morning atrioventricular block again appeared ith deglutition. The patient experienced very mild chest pain and some nausea, and shortly thereafter normal conduction returned. I travenous Isuprel was discontinued because of difficulty t the venipuncture site, and as the patient began eating lunch, intermittent complet heart block returned each time the patient swallowed medication or small sips of ater Atropine sulfate, grain 1/150 intramuscularly as administered, nd stable normal conduction persisted for the next 10 hours At this time, hile the patient was lowly sipping his morning orange juice together with his medication, there was again complete absence of trioventricular conduction for the period of five atrial systoles Fig. 2 clearly demonstrated this phenomenon Complet block as noted again on several later occasions, and there was the apparent tendency for this to be more related to cold than to warm liquids. At this time trophine sulf te, grain 1 75 intramuscularly three times daily was inst ed half hour before each meal. N further conduction defect was noted thereafter Throughout the course of the appearance of the arrhythmias no agotonic drugs ere administered Further progress otherwise uneventful. Gastrointestinal ork-up ncluding upper gastrointestinal series, barium enema, and oral cholecystogram 4 weeks later re ealed no demonstrable abnormality

Follow-up one year later revealed the patient t be in excellent health without evidence of conduction defect by electrocardiogram.

Discussion

The problem presented by this case is the relationsh p between the swallowing mechanism myocardial infarction and the appearance of atrioventricular block of high degree. In addition the patient s course emphasizes once again the advisa bility of continuous monitoring during the acute infarction period for the intermittent complete conduction defect would have otherwise probably gone unnoticed per haps allowing for a more dangerous ar rhythmia.

It appears likely that the conduction defect was at least partially related to increased vagal effect concomitant with deglutition. Although ischemia of the A-V node associated with the documented posterior infarction was very likely a contributing factor there was no suggestion on the base line electrocardiograms of

Intermittent complete heart block associated with swallowing as a complication of acute myocardial infarction

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Although it is well known that excessive vagal effects may be evident following acute myocardial infarction particularly posterior infarction the frequency and importance of this phenomenon have not been delineated The purpose of this report is to emphasize that potentially lethal conduction defects may appear as a result of vago-vagal reflexes to indicate that they may remain undetected unless brought to attention by the use of continuous monitoring and to consider the mechanism of the syndrome.

Case report

A 73-year-old retired railroad engineer with known mild diabetes mellitus, was admitted to the Coronary Care Unit with intermittent retrosternal chest pain, mild exertional dyspnea and recurrent diaphoresis of approximately one week's duration The patient had noted some radiation of the chest pain down both arms, and he specifically denied light headed sensations and syncope During the six hours prior to admission the patient noted more persistent retrosternal pain, accompanied by eructation, nausea, and vomiting unrelieved by rest and oral antiacid therapy

In review of his past history the patient did not recall previous gastrointestinal symptomatology of significance. One and one-half years prior to the present hospitalization the patient experienced an episode of ataxia and vertigo, with weakness of the left-sided extremities, all subsiding over a period of several weeks, and attributed to arteriosclerotic cerebral vascular disease.

At the time of admission the patient was described as a robust elderly male quite apprehensive without evident respiratory distress, with a slow and regular pulse, and a blood pressure in the region of 150/80 Mild arteriosclerotic changes were noted in the fundi, and the peripheral vessels were not abnormal. The lungs were clear to auscultation, and examination of the heart was not remarkable but for the notation of a soft midsystolic murmur at the apical area. The remainder of the physical examination was not remarkable

Initial and follow-up electrocardiograms revealed the changes typical of an acute evolving posterior myocardial infarction (Fig 1). Initial and later serum enzyme elevations were consistent with that diagnosis and mild fasting hyperglycemia was documented.

The patient was managed by bed rest sedation, and intravenous heparin anticoagulation. On the second hospital day an occasional ventricular extrasystole was noted, and quinidine sulfate 200 mg orally every 8 hours, was ordered. The patient's course was uncomplicated through the third hospital day and the quinidine dosage was reduced to 200 mg twice daily Continuous electrocardiographic monitoring revealed normal sinus rhythm uncomplicated by ectopic impulses. However on the fourth hospital day first degree heart block developed, followed by episodes of 2 1 atrioventricular block. Quinidine was discontinued On that day delayed A V conduction occurred as the patient was eating supper Intravenous I prel and corticoid steroid

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P R lengthening and episodic nodal ischemia related directly to swallowing seems unlikely Mackenzie[1] first published a report of this association in his description of a young patient with acute rheumatic fever who demonstrated that he could consistently produce temporary heart block by swallowing Weiss and Ferris[2] studied an individual with a traction diverticulum of the esophagus and a history of syncopal episodes initiated by swallowing Utilizing an esophageal balloon, these investigators noted that the administration of epinephrine and ephedrine prevented syncope upon distension of the esophagus despite the appearance of complete heart block while atropine sufficiently blocked the response to allow only first degree conduction delay Starling[3] described an individual with Adams-Stokes attacks and transient complete heart block during deglutition with organic disease of the conduction system documented as the block later became permanent. There seems little question therefore that a potential reflex exists which may result in defective atrioventricular conduction upon stimulation of visceral afferent vagal fibers of the esophagus. The present case indicates that this reflex is not dependent upon the existence of demonstrable esophageal pathology

The appearance of this syndrome in association with acute posterior myocardial infarction suggests that such injury causes the A V conduction system to be unusually sensitive to vagal efferent activity or that posterior infarction itself promotes vagal effect in some way A. H James[4] reported a similar case and in that instance it seemed clear that digitalis played an additive role in the appearance of complete heart block related to swallowing T N James[5] has pointed out that the vagal hyperactivity noted in cases of posterior infarction could perhaps be attributed to ischemia or injury in the region of the coronary sinus ostium an area where vagal neuroreceptors have been identified in the dog by Juhász Nagy and Szentivanyi Recently Adgey and her colleagues have emphasized the important role of vagal activity in early bradyarrhythmias such as sinus and nodal bradycardia or atrioventricular block, complicating acute myocardial infarction particularly in the posterior wall The value of atropine in the correction of early acute heart block and bradyarrhythmias was also stressed as it has been by others.[8, 9]

An interesting feature in our case which merits comment is the abrupt development of complete heart block in relation to swallowing without antecedent abnormality of the P R interval This form of atrioventricular block of the Mobitz type II variety has been described[1-11] in other patients with syncope associated with deglutition. On the other hand this particular conduction disturbance is rarely seen in recent posterior myocardial infarction which as a rule is associated with progressive P R prolongation prior to complete failure of A V transmission.[12-14] This is further suggestion that perhaps vagal influence is playing a major role in this disorder However the possibility still exists that the posterior infarction itself is contributing to a significant degree and Sutton and Davies[1] have recently suggested that materials released from nearby ischemic myocardium might be responsible for inhibition of A V nodal conduction.

Summary

A case of acute posterior myocardial infarction is reported because of the association with complete heart block, intermittent and asymptomatic, precipitated by the swallowing mechanism.

The advisability of continuous electrocardiographic monitoring of such patients is again emphasized The interplay of acute myocardial infarction, vagal effects and deglutition with A V nodal conduction is considered The abrupt development of failure of A V transmission without antecedent P R abnormality was also stressed

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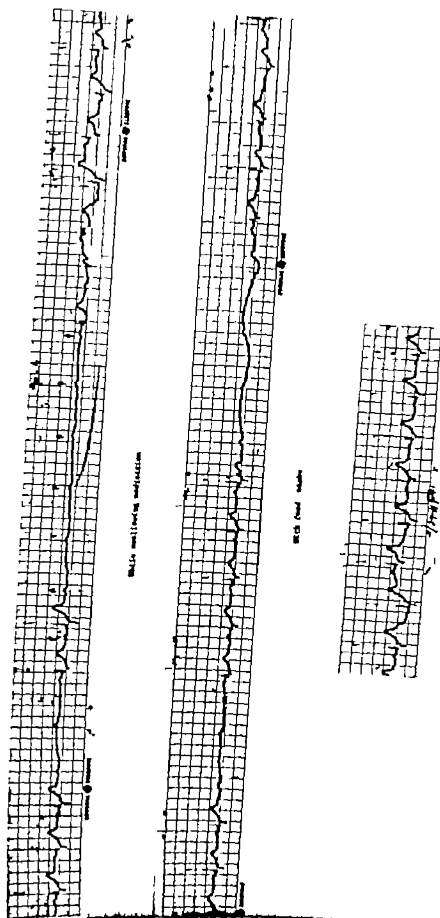


Fig 2 Electrocardiogram trips from continuous (memory loop) monitoring system demonstrating complete A V block associated with swallowing, and elimination after atropine

Review

Catecholamine metabolism in essential hypertension

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The question of whether catecholamines are involved in the etiology of essential hypertension has a long and complex history which has recently been brought into sharp focus. The story begins long ago with the discovery of epinephrine (E) in the adrenal medulla,[1,2] followed by the identification of norepinephrine (NE) and demonstration of the latter as a major neurohumor for vasoconstriction. Interwoven with this has been the development of our knowledge of the renin angiotensin aldosterone system as part of the mechanism of renovascular hypertension both experimental[3-8] and clinical.[9-12]

Numerous studies of both NE and E as well as their urinary metabolites have failed to reveal any consistently abnormal pattern in essential hypertension except perhaps for a greater than normal "scatter" of the results.[14] Physiological studies however have shown that where pressure and flow are both measured and especially when sympathetic nerve discharge is blocked patients with essential hypertension are more reactive to infused NE than normal. This was first demonstrated in the digit where work of vasoconstriction was measured. This takes into account differences in vascular structural caliber, distending pressure and critical closing pressure between the hypertensive and normotensive groups. Increased vascular reactivity in essential hypertension has also been described in the more proximal skin,[18] striated muscle [illegible] and finally in the systemic circulation as a whole.[21,22] It has also been confirmed in the digit.[23] Each of these studies is based on at least 30 patients and is highly significant statistically. An equal number of patients with hypertension attributable to renovascular and parenchymatous renal disease has been found to have normal digital vascular reactivity to NE[23,24] whereas some patients on the basis of these studies and others have been found to have both essential and renovascular hypertension.[25,26] In one study 5 out of 8 renal hypertensive patients had normal systemic vascular reactivity to NE.[22] Also patients with essential hypertension seemed to be more responsive to antihypertensive drugs than normal subjects or patients with renal hypertension of various types.[28] Reactivity in the digit[23,27] as well as in the systemic circulation[22] however was found to be increased in essential hypertension to angiotensin and in the digit also to tyramine,[29] thus complicating theoretical considerations of mechanisms.

Increased wall-to-lumen ratio in hypertension has recently again been proposed

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(E) in the endogenous denominator and possibly also in the labeled numerator of the specific activity fraction. The results obtained by the two groups, therefore although reaching the same conclusion were not strictly comparable

Gitlow and associates, however found complete one week curves of decrease in urinary specific activity of NE and metabolites altered profoundly and in different ways by reserpine (3 cases)[41] and by guanethidine (2 cases)[41] Similar profound and varied changes in the early (48 hour) specific activity urinary decay curves in NE and VMA after labeling NE stores with H DOPA were reported in essential hypertensive subjects by DeQuattro and Sjoerdsma[44] after reserpine (2 cases) alphamethyl tyrosine (3 cases) and pargyline hydrochloride (2 cases) administration.

Meanwhile in 1967 and 1968 Wolf and associates[45-46] reported that a single injection of tritiated NE resulted in a decreased apparent secretion rate" of NE in essential hypertension. This was measured by dividing the counts of H NE administered intravenously in a single dose by the specific activity of its metabolite normetanephrine (NM) in a 24 hour urine specimen collected after the injection The chief factor in this decreased value however was a greater excretion of H NM in essential hypertension (20 cases) than normal (20 cases) The differences were highly significant statistically DeQuattro and Sjoerdsma, however in 1968 left the impression that there was nothing wrong with catecholamine metabolism in essential hypertension. What is more Wolf and coworkers found that the secretion rate was normal in renal (5 cases)[46] and renovascular hypertension (5 cases)[46,48] In pheochromocytoma patients the apparent NE secretion rate was above normal largely because of increased values for endogenous nonlabeled NM in the urine (4 cases)[46] The dose of racemic tritiated norepinephrine (DL-β-H NE) used was 40 μg (1 mc.) in these studies and at this dose they could find no difference in the total H counts in the 24 hour urine collected after the injection between essential hypertensive and normotensive groups. Also only about 1/400 of the administered H NE radioactivity was found in urinary H NM indicating that any difference in NM specific activity would be highly diluted and obscured by the excretion of H^3 NE itself and other labeled metabolites.

Meanwhile Gitlow and associates[41] were evaluating NE metabolism by administering various doses of H NE in single intravenous injections in order to ascertain whether or not a specific segment of NE handling in the patient with essential hypertension differed from that of the normal They found that, at a dose of 8 μg (200 μc) of H^3 NE, the urinary excretion of tritium itself and hence the sum of the labeled NE and all its labeled metabolites by the patient with essential hypertension (15 cases) was greater than normal (15 cases) ($p < 0.01$) Again the renovascular (2 cases) and renal hypertensive patients (1 case) fell into the normal group. The three pheochromocytoma cases studied with this test fell into the hypertensive range. The separation between normotensive and essential hypertensive subjects was sharp but disappeared as the dosage of H^3 NE administered was increased. Differences in renal clearance of H^3 after administration of H^3 NE did not appear to explain the variations in H^3 excretion between the essential hypertensive and normotensive subjects. All these findings were consistent in nonuremic patients only It should also be emphasized that blood pressure was transiently increased by about 20 mm Hg in the Wolf experiments[45-48] but not influenced at all by those of Gitlow and associates.[41]

What does all this mean with reference to mechanisms in essential hypertension? Perhaps it would be better to indicate what the observations do not mean. The decreased apparent NE secretion rate due to increased excretion of H^3-NM after intravenous H^3-NE described by Wolf and co-workers[45-48] and the increased excretion of H after intravenous injection of H NE described by Gitlow and associates[41] are probably not hemodynamic since no blood pressure elevation was produced with the dose used by the latter group Also elevated blood pressure per se is not responsible for the findings since they are absent in renovascular and renal hypertension and in transient hypertension produced by

as a major cause for increased vascular reactivity.[19,20] That such structural changes exist has been known for some time[21-23] and they may be responsible for increased vascular response to stimuli under certain conditions. This hypothesis, however, fails to explain normal responsiveness to stimuli in renal and renovascular hypertension[23,24] and in Raynaud's disease[25] where there are also increased vascular wall-to-lumen ratios. What is more, the errors inherent in comparing percentage change in resistance in groups with different structural starting vascular lumina and different internal distending pressures have been emphasized many times.[26,27] Granting, however, that percentage changes in resistance have some validity, one would have to conclude that responsiveness on a biochemical basis in renal and renovascular hypertension is less than normal. The wall-to-lumen ratio hypothesis also fails to explain how the increased ratio comes about in hypertension. If wall hypertrophy is the major factor, is this not caused by increased vasoconstriction and hence by smooth muscle hypertrophy due to increased work load? It seems farfetched to postulate an inherent increase in hypertrophy because of altered mesenchymal tissue responding excessively to normal work loads.[30] If the theory of increased cardiac output as an initiating factor causing vasoconstriction because of vascular autoregulation[33] is assumed, what causes the increased cardiac output and why is there increased reactivity in the digit[17,21] where the major circulation is through arteriovenous anastomoses largely sympathetically controlled rather than through precapillary sphincters, admittedly more subject to autoregulation? It must also be pointed out that increased vascular reactivity is a very early phenomenon in essential hypertension[34] and is even found in essential prehypertension[35] and that such reactivity can be increased in a few weeks at most by the administration of steroids[40,41] and such drugs as guanethidine[42] as well as decreased by such drugs as thiazides[43] and spironolactone.[44] These changes, considering their magnitude and the speed of their development, can hardly be attributed to changes in vascular wall-to-lumen ratios. For all these reasons, the phenomenon of increased vascular responsiveness in essential hypertension must in part at least be considered to be of biochemical rather than structural origin.

That such biochemical factors can be operative was first demonstrated by Gitlow and associates who found that the disappearance rate of H^3 NE and its metabolites in plasma, measured from 4 to 24 hours after its infusion intravenously, was more rapid in patients with essential hypertension than in normotensive subjects.[45,46] They studied five patients in each group extensively ($p < 0.05$) but since then have confirmed this in several other patients.[47] Later these workers studied the rate of decreasing specific activity of urinary H^3 NE and its metabolites after infusing H^3 NE intravenously for one hour in 11 subjects and delineated at least three different exponential components with $t^{1/2}$ (time of decrease of half the specific activity) of 1.2, 5.2, and 24.6 hours, respectively.[47-49] A steady state was reached only during the third phase.[49] A similar $t^{1/2}$ for the final steady state was also described by Chidsey and associates.[50] Gitlow and associates[47] found no significant difference from the normal in the $t^{1/2}$ during the first 48 hours and also during one week after infusion in four essential hypertensive patients but did not publish these negative results. In 1967 and 1968, DeQuattro and Sjoerdsma[51,52] studied the $t^{1/2}$ of the specific activity of urinary NE and vanillylmandelic acid (VMA) after labeling the stores with tritiated dihydroxyphenylalanine (H^3 DOPA). They used L-H^3 DOPA instead of the racemic compound and presumably selectively labeled the levorotatory stores of NE. Since a maximally permissive amount of H^3 DOPA had to be given in order to obtain counts in the urine which were meaningful, the change in specific activity could be measured by these authors only for less than 48 hours. It is clear, therefore, that they had not reached a steady state. They, too, like the Gitlow group, found no difference between normal (5 subjects) and hypertensive subjects (6 cases) in the portion of the curve which they measured. DOPA, however, penetrates the blood-brain barrier whereas NE does not and the specific activity of VMA is contributed to by epinephrine

anxiety[39,40] In addition analysis of sequential 3 hour urine collections indicates that increased excretion of H³ NM in essential hypertension persists for the entire 24 hours after the injection of H³ NE[58] The phenomenon is probably not renal since renal clearance of H³ after H³ NE administration is similar in normal and essential hypertensive subjects.[41] The effect is not due to increased vascular response occasioned by the accumulation of angiotensin in the neural and vascular stores and its release by neural activity[63] because increased vascular reactivity is demonstrated best when neural activity is blocked regardless of the vasoactive stimulus[34] This same explanation would also not account for the biochemical findings of Wolf and associates[39,40] and Gitlow and coworkers[41] in essential hypertension and would be contrary to the negative findings as to reactivity[23,24] and excretion of H³ NE metabolites in renovascular and parenchymatous renal hypertension[44,41] The best explanation of the findings is that there is a block or relative block in uptake and/or storage of H³ NE or of NE in essential hypertension Does this mean that there is a block in re-entry into the stores as well as in entry? In other words since a certain amount of NE which is released from neural stores goes back into these stores[44] is this process also partially or completely blocked? And if this is so why are the urinary decay curves of the specific activities of NE and its metabolites in essential hypertension previously found by Gitlow[47] and reported by DeQuattro and Sjoerdsma[48] no different from the normal

The answer to this question is surely methodological For one thing it is possible that only the NE pool which is subjected to O-methylation as the first step in degradation is abnormal in essential hypertension[45,46] If H³ DOPA is administered[41,43] the effects in this O methylation pool are diluted by NE metabolized in the brain where monamine oxidation may be the first step in degradation[48] and possibly by NE and its metabolites from the adrenal medulla liver and heart or from extraneuronal stores in general. If the specific activity of VMA is measured this is a metabolite of E as well as of NE[44] and a significant difference in NE metabolism would again be diluted How important a role the liver heart, and brain play in the degradation process at different doses is not known It is probable that they and the extraneuronal stores play a proportionately larger role at increasing doses and since they are relatively less involved in sympathetic vasoconstriction this obscures the NE metabolism in tissues more involved It is also not known whether different doses of labeled NE or labeled DOPA metabolized to NE affect synthesizing and/or degrading enzymes differently It is well known however that a defective metabolic step can be obscured in a multipool system by an investigative technique that lumps together the normal and abnormal metabolism of the substance studied

As to pool size the inference from the studies by Wolf and associates[39] that the NE pool is smaller than normal in essential hypertension applies only to that pool into which the label is distributed and which is converted to NM during a 24 hour period This inference may or may not be applicable to the total body NE content Moreover that pool into which injected H³-NE is taken up during the first 24 hours and converted to H³ NM may well be a critical one from a functional standpoint Surely it is more important to study the *differences* between normal and essential hypertensive subjects in their handling of NE than to emphasize the similarities.

How do these studies fit in with those of experimental hypertension? Renal hypertension is an acquired disease but essential hypertension in man is definitely hereditary[47,48] Hereditary hypertension has been described in rats and it was hoped that this model would be more analogous to that of essential hypertension in man There appear however to be several types of hereditary hypertension in rats one sodium sensitive[69] and one not[70] and although the former group is more reactive to NE even before hypertension has developed[71] the latter group seems to have a larger pool of cardiac NE than normal[72] There is a third colony of hereditary hypertensive rats also hyperreactive to NE which may have still different characteristics.[73] To complicate the picture further the sodium sensitive hereditary hypertensive rats seem

to have a humoral component which can be transferred by parabiosis.[73] Also desoxy corticosterone (DOC) and salt hypertension in rats produces a decreased store of NE in their tissues and this effect can be blocked by chlorisondamine which blocks neural transmission at the sympathetic ganglia.[74]

All this again emphasizes the dictum that the proper study of man is man him self The studies in man implicate NE metabolism at the vascular receptor and neurovascular storage sites in essential hypertension despite the many questions which are still left unanswered.

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Fundamentals of clinical cardiology

Cardiac positions

A Primer

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The interrelations of cardiac chambers, great vessels, other viscera, and the direction of the cardiac apex are subject to a limited number of variations and should be easily mastered. In fact, students recoil from the subject as inordinately complex and the literature does seem complex. Authors insist on an understanding of the embryology of the various arrangements as a prerequisite for discussion, an insistence not justified by the depth of our current knowledge. Terminology is chaotic. This paper, which is devoid of any original thought, reviews the combinations and permutations of cardiovascular visceral alignments, presents a classification which masquerades in different guises but seems to be nearly universal, and offers an abbreviated glossary. The bibliography is intended to serve as a guide to the recent contributors in the field[1-6] and their references will lead the reader to the world's literature in depth. Emphasis is placed on acquainting the neophyte with the basic concept of cardiac positions and with the language encountered in reading and talking about the subject.

I. Anatomy and terminology

A. Cardiac chambers. Imagine yourself inside a heart. You must be able to identify the specific chamber with no knowledge of your position in space. Finding the limbus and fossa ovalis indicates that you are on the secundum side of the atrial septum. Identification of the orifices of the superior and inferior vena cava and the coronary sinus offers further assurance that you are in the right atrium (RA). Conversely, identification of the septum primum and four pulmonary vein orifices is assurance that you are in the left atrium (LA). Passing through a tricuspid valve into a chamber with trabeculations on all walls, you are in the right ventricle (RV). Conversely, passing through a bicuspid valve into a chamber with two prominent papillary muscles anchored opposite a nontrabeculated septal wall places you in the left ventricle (LV). In this context, left and right have no spatial significance. If you have both male and female acquaintances named Chris, you will be able to think of either Chris without sex being a problem—unless there is emotional involvement! Just so, if you remain emotionally uninvolved, you will have no problem recognizing a right ventricle anywhere.

Mathematically, 720 possibilities exist for connecting the four cardiac chambers and two great vessels. Anatomically there are only four possibilities since the align

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ment must begin right atrium (the right atrium anchors the system since by definition, it receives the systemic venous return and, indeed almost always receives all or a major portion thereof) then ventricle then great vessel. Bear in mind that we are not yet ready to consider intrathoracic position or relation to other viscera and have no concern for complicating anomalies such as shunts, obstructions or unusual connections of vessels other than aorta (Ao) and pulmonary artery (PA). The four possibilities are

RA → RV → PA LA → LV → Ao
RA → RV → Ao LA → LV → PA
RA → LV → PA LA → RV → Ao
RA → LV → Ao LA → RV → PA

Consider these pathways and put a name which is meaningful to you on each of the four. Experience with radiologists and cardiologists in training suggests that there would be universal agreement on RA → RV → PA = *normal*. RA → RV → Ao evokes a majority vote in favor of complete transposition of the great vessels, *transposition* for short. RA → LV → PA is well understood by all as physiologically corrected transposition of the great vessels, *corrected transposition* for short. Authors who object because some concomitant lesion may leave the circulation physiologically deranged uniformly use corrected *transposition* parenthetically to explain their own terminology. RA → LV → Ao evokes no response this is understandable since there are apparently *fewer than five well-documented cases* in the world literature. *Ventricular transposition* (see Glossary) follows the example set by transposition of the great vessels. To summarize

RA → RV → PA Normal
RA → RV → Ao Transposition
RA → LV → PA Corrected transposition
RA → LV → Ao Ventricular transposition

One of these four alignments is found in all hearts. This fact is unaltered whether the cardiac apex points leftward rightward or is midline and whether there is situs solitus (usual placement of viscera) or situs inversus (right left reversal of viscera).

B The cardiac apex and visceral situs The following possible combinations exist

Leftward apex with situs solitus
Leftward apex with situs inversus
Rightward apex with situs solitus
Rightward apex with situs inversus
Midline apex with situs solitus
Midline apex with situs inversus

Begin with number four on the list rightward apex with situs inversus or situs inversus totalis. The mirror-image man has always fascinated investigators and has served as fulcrum for most classifications of cardiac positions. Thus consensus dictates that rightward apex with situs inversus equals mirror-image dextrocardia, *dextrocardia* for short. Having taken this all important step rightward apex with *situs solitus* becomes dextroversion and the rest follows

Leftward apex with
situs solitus = normal (levocardia)
Leftward apex with
situs inversus = levoversion
Rightward apex with
situs solitus = dextroversion
Rightward apex with
situs inversus = dextrocardia
Midline apex with
situs solitus = mesocardia
Midline apex with
situs inversus = mesoversion

This classification is consensus terminology aimed at facilitating communication with others and understanding the literature. Logic dictates that we reverse dextrocardia and dextroversion so that version in the name would always indicate situs inversus and cardia, situs solitus. However logic *did not give birth to a word like dextroversion* and no amount of logic will bury it. Since any of these six apex-situs alignments may be found with any of the four internal alignments already enumerated the foundation has been laid for consideration of 24 hearts (see Table I). If mere *numbers constitute a problem* bear in mind that in a lifetime of practice outside of a cardiac specialty one is likely to encounter only five of these hearts (*normal* transposition, corrected transposition dextrocardia, and dextroversion with corrected transposition).

C The great vessels Before leaving the numbers game prepare for one last proliferation. The aorta and pulmonary artery regardless of their ventricular connections, may vary in their relationship to one

Nomenclature			Blood Flow	Intrathoracic Relationships
normal	left sided heart with situs solitus	levocardia I solitus	RA→RV→PA	
transposition	c̄ noninverted transposition	II	RA→RV→Ao	
corrected	c̄ inverted transposition	III	RA→LV→PA	
ventricular	c̄ isolated ventricular inversion	IV	RA→LV→Ao	
levoversion	left sided heart with situs inversus	levocardia IV inversus	RA→RV→PA	
c̄ transposition	c̄ noninverted transposition	III	RA→RV→Ao	
c̄ corrected	c̄ inverted transposition	II	RA→LV→PA	
c̄ ventricular	c̄ isolated ventricular inversion	I	RA LV→Ao	
dextroversion	right sided heart with situs solitus	dextrocardia I solitus	RA→RV→PA	
c̄ transposition	c̄ noninverted transposition	II	RA→RV→Ao	
rrected	c̄ inverted transposition	III	RA→LV→PA	
c̄ ventricular	c̄ isolated ventricular inversion	IV	RA→LV→Ao	
dextrocardia	right sided heart with situs inversus	dextrocardia IV inversus	RA RV PA	
c̄ transposition	c̄ noninverted transposition	III	RA→RV→Ao	
c̄ corrected	c̄ inverted transposition	II	RA→LV→PA	
c̄ ventricular	c̄ isolated ventricular inversion	I	RA LV→Ao	
mesocardia	midline heart with situs solitus	mesocardia I solitus	RA RV→PA	
c̄ transposition	c̄ noninverted transposition	II	RA→RV→Ao	
c̄ corrected	c̄ inverted transposition	III	RA→LV→PA	
c̄ ventricular	c̄ isolated ventricular inversion	IV	RA→LV→Ao	
mesoversion	midline heart with situs inversus	mesocardia IV inversus	RA RV→PA	
c̄ transposition	c̄ noninverted transposition	III	RA→RV→Ao	
c̄ corrected	c̄ inverted transposition	II	RA→LV→PA	
c̄ ventricular	c̄ isolated ventricular inversion	I	RA→LV→Ao	

Table I Cardiac positions. The first column contains the consensus terminology explained in the text. Next is the work of Rosenbaum and, finally, a scheme derived from the work of the Van Praaghs. The fourth column indicates the alignment of the cardiac chambers and the great vessels. Note that the four basic alignments are repeated for each of the six possible apex-situs combinations. The last column is schematic of the various hearts (boxes) as seen from the front and the aorta pulmonary artery relationship (cartwheels) at the valve level as seen from above. The arrows attached to the boxes indicate the direction of the cardiac apex. Reading across, each box corresponds to two lines in each of the first four columns. Looking down the schematic column, note that there are four basic hearts repeated three times with different apex directions. The aortic position rotates around the pulmonary artery for each of the four adjacent hearts as indicated by the curved arrow on the cartwheels—clockwise for situs inversus and counterclockwise for situs solitus. One of the cartwheels is marked with Roman numerals to show how the positions coincide with the terminology derived from the Van Praaghs. The name in each line of the first three columns assumes a great vessel relationship as indicated by the adjacent cartwheel. If such is not the case what happens is additional verbiage in columns 1 and 2 and a very complex situation in column 3 a scheme which has no built in guarantee of the cardiac great vessel alignment (see Fig 6).

The aortic pulmonic relationship predicted for ventricular transposition is theoretical. Too few cases have been reported for verification.

another at the valve level The aortic valve may lie anywhere on a full circle around the pulmonary valve The accepted simplification is illustrated by the PA → Ao cartwheels in Table I showing quadrated circles with Roman numerals assigned the quadrants. Thus we have 24 hearts each with four possible great vessel relationships for a theoretical total of 96. But take heart (no pun intended) there is a predicted great vessel relationship for each of the 24 hearts and significant variations from the expected are unusual Five hearts will still cover most situations.

II Diagnosis

A Physical examination Inspection palpation percussion and auscultation may reveal the position of the main cardiac activity the liver and the stomach but the physical examination is non specific and usually less accurate than the other modalities under discussion

B The electrocardiogram (ECG) (*Figs 1 and 2*) In the absence of a left atrial ectopic rhythm [7] a left sided SA node with asplenia[8] or the asplenia polysplenia syndrome with uncertain visceral situs P wave analysis determines the atrial locations with great accuracy A leftward inferior P vector with an inverted P wave in Lead aV_R and an upright P wave in Leads I and V_6 indicates normal atrial location A rightward inferior P vector with an inverted P wave in Leads I and V_6 and an upright P wave in Leads aV_R and V_{1R} indi

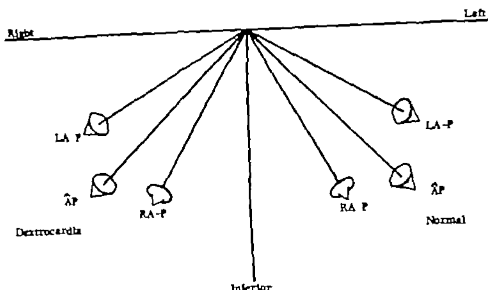


Fig. 1. Initial right atrial (*RA P*), terminal left atrial (*LA P*), and mean P vectors (*ÂP*) of the normal heart and of dextrocardia (situs inversus totalis) without coexistent defects.

cates situs inversus arrangement of the atria. Ventricular localization by analysis of QRS complexes and T waves has proved less reliable than atrial localization but certain empirical electrocardiographic observations may be helpful.

NORMAL. The normal ECG will not be described but has been illustrated for comparison with the ECG's of other cardiac positions.

TRANSPOSITION. The P vector is usually leftward and inferior (normal) but the magnitude often suggests right atrial enlargement. The QRS and T vectors may vary somewhat with the type of accompanying defects and the status of the pulmonary vascular resistance, but usually right axis deviation and right ventricular enlargement with a leftward inferior anterior T vector are present.

CORRECTED TRANSPOSITION. The P vector is normal. The P wave may be tall and notched in Lead II with varying degrees of atrioventricular block (long P-R interval, 2:1 block, or complete atrioventricular block). The ventricular portion of the conduction system is inverted or reversed; therefore ventricular inversion may be suspected when the sequence of depolarization and repolarization is unusual. The initial QRS vector is most often unusually leftward and superior giving a ... ence of expected initial V and qV). The ÂQRS in the frontal plane will be rightward or normal with qR III due to a rightward inferior terminal *QRS* vector in most cases. *Left* axis deviation (270 to 330 degrees) due to a leftward superior terminal QRS vector is occasionally seen.[1] In the absence of clinical right ventricular enlargement, an upright T wave in V in children may be due to ventricular inversion.

DEXTROCARDIA. The ECG of situs inversus totalis with RA → RV → PA blood flow (normal) is illustrated. It is not necessary to reverse the arm leads in order to analyze the dextrocardia ECG and compare it with normals—this may be done mentally since aV_R is the equivalent of aV_L, II of III, V_1 of V_2, V of V_{3R}, V_{4R} of V_4, etc. It is advisable to record V_{3R} through V_{6R} leads to allow measurement of QRS magnitudes.

DEXTROCARDIA WITH CORRECTED TRANSPOSITION. This physiologically normal heart is rare but the ECG changes are predictable. Varying degrees of atrioventricular block may occur. *Usually the ÂQRS would* be leftward or normal (60 to 80 or 90 to 210 degrees, respectively for dextrocardia) with a rightward superior initial vector creating qV and RV_{6R} deflections (absence of expected rV_1 and qV_{6R}) and a leftward, inferior terminal vector causing a qRII record. Occasionally the ÂQRS

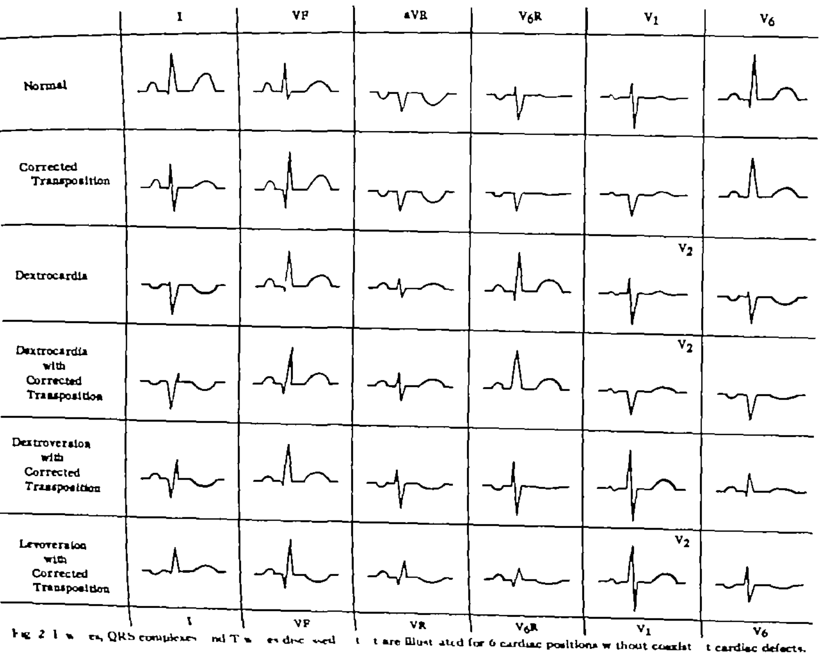


Fig. 2. P waves, QRS complexes, and T waves described in text are illustrated for 6 cardiac positions without coexistent cardiac defects.

would be between 210 and 270 degrees in the *frontal plane*. Of course, the P wave would be inverted in Lead I and V_6 and upright in aV_R and V_{4R} (the expected P vector for situs inversus).

DEXTROVERSION WITH CORRECTED TRANSPOSITION. These patients usually have complex, often severe coexistent congenital heart disease; therefore, the ECG changes are rather variable and depend on the type and severity of the underlying defects. Since this entity is one of the more commonly recognized abnormal cardiac positions, certain ECG changes have proved helpful. The P vector is normal and thus the P wave remains upright in Leads I and V. Lead I usually shows a qR or qs deflection with (more often) or without T inversion. Lead V often reveals RS complexes and the T wave is usually upright in all V leads.

LEVOVERSION WITH CORRECTED TRANSPOSITION. This rare cardiac position is usually associated with the asplenia-polysplenia syndrome[4] and therefore is usually accompanied by uncertain atrial location, complex congenital cardiac lesions, and thus complicated ECG changes; however the hypothetical ECG is shown. The P wave would be inverted in Leads I and V and upright in aV_R and V_{4R}.

The subtle positional differences between the midline hearts and their left or right apical counterparts are not usually detectable electrocardiographically.

C. The PA chest film. The cardiac apex usually can be located by inspection and will be on the side of the low hemidiaphragm.[11] If both of these criteria fail, the apex is probably midline. A left-sided *stomach bubble indicates situs solitus*; a right-sided stomach bubble, situs inversus. A few exceptions have been reported but *the stomach bubble is more accurately* identified than the more reliable liver, and the descending aorta is considerably less reliable (e.g., 25 per cent of right descending aortas in patients with tetralogy of Fallot and normal cardiac position). In summary, which of the six apex-situs combinations exists is easily determined from the chest film (Fig. 3).

Normal	Left apex, left stomach bubble
Levoversion	Left apex, right stomach bubble
Dextrocardia	Right apex, right stomach bubble
Dextroversion	Right apex, left stomach bubble
Mesocardia	Midline apex, left stomach bubble

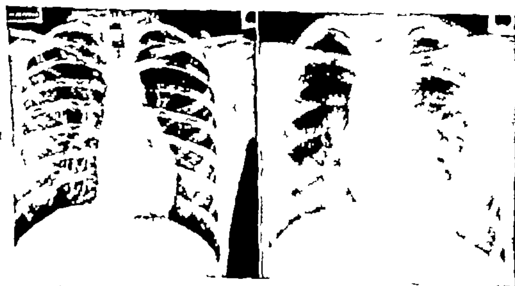


Fig. 3. A and B. A, Normal—left apex, left stomach bubble (see Fig. 7). B, Levoversion—left apex, right stomach bubble.



Fig 3 *C* and *D* *C* Dextrocardia—right apex, right stomach bubble. *D* Dextroversion—right apex, left stomach bubble



Fig 3 *E* and *F* *E*, Mesocardia—midline apex, left stomach bubble. *F* Mesoversion—midline apex, right stomach bubble (see Fig 8). In these cases situs of aorta and stomach bubble agree. Coexisting anomalies present in all except *E*.

Mesoversion Midline apex, right stomach bubble

Loss of the pulmonary artery contour with normal or increased pulmonary vascularity should suggest transposition if the vascular pedicle is narrow or corrected transposition if the pedicle is broad and sloping The narrow pedicle of transposition results from the pulmonary artery lining up behind the aorta The sloping contour of corrected transposition results from the aorta ascending on the same side as the arch (Figs. 3 *A* and 7)

This short dissertation fails to do justice to the information available from intelligent interpretation of the chest film but



Fig 4 Dextroversion. Catheter identifies right-sided inferior vena cava which, with reflux of contrast medium into hepatic veins, identifies normally positioned but elongated right atrium.



Fig 5 Contrast medium confined to atria in patient with tricuspid atresia and atrial septal defect. Sitting-duck or decoy appearance of left atrium in diastole. Lateral projection shows anterior projection of normally positioned atrial appendages Compare right atrium with appearance in Fig 4

is in keeping with the scope of this paper and the need for cardiac catheterization and angiocardiography for final evaluation

D The abdominal film Determination of situs in the rare patient with abdominal heterotaxy will be greatly aided by an abdominal film obtained while there is contrast medium in the stomach and colon

E. Spleen and liver scanning A number of nuclide techniques are now available for definitive localization of the liver and spleen Colloidal particles less than one micron in diameter tagged with an appropriate photon emitter and injected intravenously will be phagocytized by reticuloendothelial cells so that a scan of the

abdomen will demonstrate the liver (e g colloidal gold 198) or liver and spleen (technetium 99m sulfide) The position of the spleen polysplenia or asplenia may be determined without confusing emissions from the liver by a scan following an intravenous injection of chromium 51 tagged red cells which have been injured so that they will be collected rapidly in any available splenic tissue.

F Angiocardiography Angiocardiography should be part of a complete cardiac cathe-

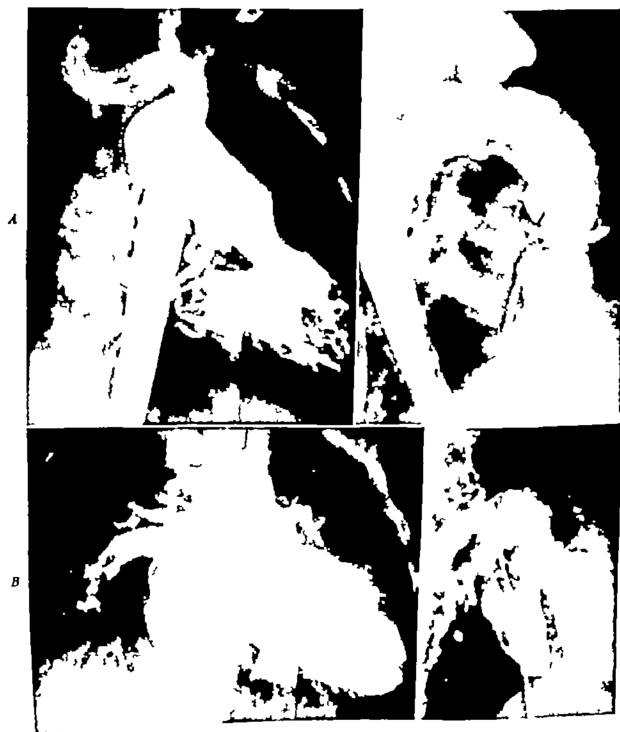


Fig 6 Transposition (RA → RV → Ao) with anterior and leftward aorta (great vessel position usually found with corrected transposition position III of Van Praagh) *A* Right ventricular injection shows the coarse trabeculations and infundibular outflow tract of that chamber *B* Left ventricular injection with catheter flipped back into left atrium. Frontal projection shows smooth elliptical outline of left ventricle lateral projection, ventricular septum on edge and posterior position of pulmonary artery

terization study. The physiologic data permit quantitative evaluation of associated shunts or obstructive lesions and the contrast medium studies demonstrate the anatomy. Since this discussion is concerned only with cardiac positions, attention is confined to the latter except to note that the course of the catheter may be very helpful in localizing the great vessels, particularly the venae cavae. The entrance of the catheter into the heart identifies the right atrium (Fig. 4). During the early phase of the levogram the pulmonary veins look like the legs and the left atrium the body of a crab (Fig. 9, *B*). The sitting duck appearance of a well-opacified left atrium (Fig. 5) might not be so apparent for cardiac positions other than normal. The right ventricle is most reliably recognized by its coarse outline (Fig. 6, *A*). Conversely, the left ventricle is spade shaped or elliptical and the outline is smooth (Figs. 6, *B*, 7, 8, and 9, *B*). The relationship of the aorta and pulmonary artery will be outlined clearly by a biplane study. Analysis of this relationship may help to identify the ventricles. For instance, in a patient with situs solitus, a leftward anterior aorta is corrected transposition position; hence the right ventricle should be leftward. In other words, the ascending aorta and right ventricle should be on the same side (Figs. 7 and 8). This criterion fails when the predicted great vessel relationship fails (Fig. 6). On the other hand, the higher of the two semilunar valves should reliably identify the right ventricle (elevated by the infundibulum).

The relationship of one atrium to the other and one ventricle to the other should not be of great concern. In the normal heart the right chambers are mostly anterior and only slightly rightward. Both the right-left and the anterior-posterior relationships may vary and a caudocranial factor may be introduced with either ventricle lying on top of the other (Fig. 9). The side of the cardiac apex, the visceral situs, and the atrial-ventricular-great vessel alignment are the crucial diagnostic features.



Fig. 7. Corrected transposition (RA → LV → PA but with ventricular septal defect and supravalvular pulmonary stenosis). Rightward, smooth, elliptical left ventricle from which pulmonary artery arises. Leftward (and anterior) aorta faintly opacified. Apex points leftward. Same case as Fig. 3, *A*. See Fig. 8.



Fig. 8. Mesoversion with corrected transposition (with ventricular septal defect and subpulmonic stenosis). Same case as Fig. 3, *F*. Contrast with levocardia with similar defects illustrated in Figs. 3, *A* and 7.

Discussion

There is one unavoidable complexity in the study of cardiac positions. If the situ

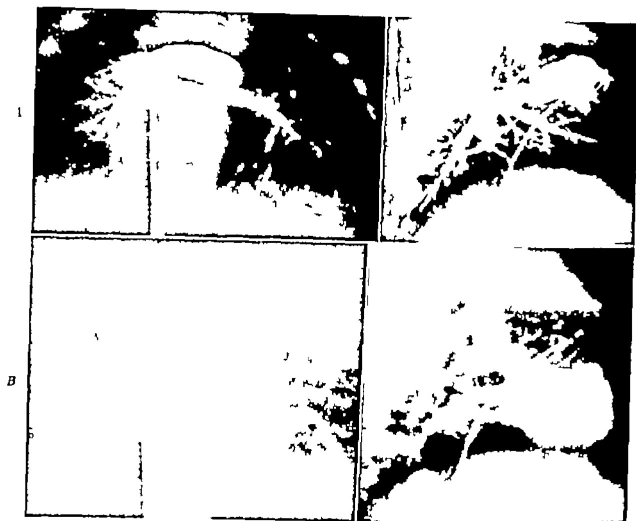


Fig 9 Dextroversion with no complicating defect. T p of catheter in right ventricle 1 Dextrogram, frontal and lateral. *B* Levogram, frontal and lateral. Apices of both entricles to extreme right with right entricle on top of left ventricle

dent needs to understand how something came to be in order to deal with the end result he will be frustrated Logic dictates that whatever determines visceral situs should determine the relationship of the cardiac chambers and the direction of the cardiac apex. In fact there is only a statistical relationship between the three variables with one exception the atria behave like noncardiac viscera and reliably correspond to situs. Thus with situs solitus the atria will be in their usual location whether the cardiac apex is leftward (normal) rightward (dextroversion) or midline (mesocardia) Conversely the right atrium will be on the left and the left atrium on the right with situs inversus whether the apex is to the right (dextrocardia) left (levoversion) or midline (mesoversion) If visceral situs is indeterminate (Ivemark s syndrome asplenia polysplenia) identification of the atria likewise may be indeterminate The unpredictability of the cardiac apex is well illustrated by this syndrome of symmetry The stomach is midline the liver stretches evenly across the abdomen the lungs mimic one another and the cardiac apex is on the left, occasionally on the right seldom midline The bending of the rapidly growing primitive cardiac tube may determine the situs of the ventricles but why it bends right or left and particularly why the ultimate ventricular relationship fails to determine the direction of the apex remain mysteries. However physicians are used to playing the name game We are comfortable once we establish a diagnosis of sarcoidosis, not because we understand the disease but because the diagnosis allows us to prognosticate Recognition of cardiac positions has both diagnostic and prognostic merit

The normal position and dextrocardia have less than 5 per cent coincident congenital heart disease.[3] Dextroversion is usually associated with corrected *transposition and* has a high incidence of defects in septation. Corrected transposition places the tricuspid *valve in the outflow* of the left atrium so that Ebstein's anomaly will simulate mitral disease. Hearts with corrected transposition are likely to have a coronary artery[12,13] just where a ventriculotomy might otherwise be done. *Levoversions, the few dextrocardias* with associated defects, and hearts which defy classification tend to have defects which are life-threatening and uncorrectable by present techniques.

Summary

A study of the current concepts of cardiac *positions reveals that there are 96 possi*bilities. One needs to understand that returning systemic venous blood may reach either the aorta or pulmonary artery always by the right atrium but thence either *by the right or left ventricle (four basic* alignments) that the cardiac apex may be anywhere from left to right that visceral situs may be normal, reversed, or indeterminate and that the aorta may swing *on a full circle around the* pulmonary artery. Terminology based on embryologic considerations is confusing descriptive terminology is cumbersome, and classical terminology is illogical. A guide through this maze is presented and the simplicity of the basic anatomic facts is emphasized. The ECG and chest film are the most reliable routine diagnostic tools but selective angiocardiography is necessary for definitive diagnosis.

We are indebted to the Department of Radiology, Fitzsimons General *Hospital, Denver, Colo.* for the films reproduced in Fig. 3, *A* and 7.

Dr. Stern Granda spent electi... time on this project during his fourth year in medical school.

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Glossary

Anatomically corrected transposition. See *ventricular transposition.*

Aortic ventricle. Ventricle which gives rise to the aorta. The anatomy of the ventricle and its atrial connection are not identified. Synonyms: arterial ventricle, systemic ventricle.

Arterial ventricle. See *aortic ventricle.*

Asplenia. Absent spleen associated with symmetrical liver and lungs and major intracardiac anomalies—usually defects



Fig 9 Dextroversion with no complicating defect. Tip of catheter in right ventricle. A Dextrogram, frontal and lateral B Levogram, frontal and lateral. Apices of both ventricles to extreme right with right ventricle on top of left ventricle

dent needs to understand how something came to be in order to deal with the end result, he will be frustrated Logic dictates that whatever determines visceral situs should determine the relationship of the cardiac chambers and the direction of the cardiac apex. In fact there is only a statistical relationship between the three variables with one exception the atria behave like noncardiac viscera and reliably correspond to situs. Thus with situs solitus the atria will be in their usual location whether the cardiac apex is leftward (normal) rightward (dextroversion) or midline (mesocardia) Conversely the right atrium will be on the left and the left atrium on the right with situs inversus whether the apex is to the right (dextrocardia) left (levoversion) or midline (mesoversion) If visceral situs is indeterminate (Ivemark s syndrome asplenia polysplenia) identification of the atria likewise may be indeterminate The unpredictability of the cardiac apex is well illustrated by this syndrome of symmetry The stomach is midline the liver stretches evenly across the abdomen the lungs mimic one another and the cardiac apex is on the left occasionally on the right seldom midline The bending of the rapidly growing primitive cardiac tube may determine the situs of the ventricles but why it bends right or left and particularly why the ultimate ventricular relationship fails to determine the direction of the apex remain mysteries. However physicians are used to playing the name game We are comfortable once we establish a diagnosis of sarcoidosis not because we understand the disease but because the diagnosis allows us to prognosticate Recognition of cardiac positions has both diagnostic and prognostic merit

with physiological atrioventricular-great vessel alignment. Another approach to classification of corrected transpositions.[14]

Isolated dextrocardia. See *dextroversion.*

Isolated levocardia. See *levoversion.*

Isolated ventricular inversion. See *ventricular transposition.*

L-loop. Right ventricle to left of left ventricle—cardiac apex may be anywhere. Synonyms: Situs inversus of ventricles; inverted ventricles.

Left atrium (LA). Atrium which receives pulmonary veins and has septum primum. The left has no spatial significance.

Left ventricle (LV). Ventricle which has mitral atrioventricular valve, two large papillary muscles, and a smooth septal wall. The left has no spatial significance.

Levocardia. (1) Left cardiac apex with usual visceral position. Synonyms: normal; situs solitus. (2) Left cardiac apex without the additional implications of the first definition.

Levoposition. Leftward displacement of the heart due to extracardiac factors.

Levotransposition (l-transposition). The aortic valve is to the left of the pulmonary valve. Usually occurs with l-loop in which case same as corrected transposition with situs solitus or transposition with situs inversus.

Levoversion. Left cardiac apex with reversed atrial alignment (situs inversus). Synonym: isolated levocardia.

Mesocardia. (1) Midline cardiac apex with usual visceral position (situs solitus). (2) Midline cardiac apex without the additional implication of the first definition.

Mesoversion. Midline cardiac apex with reversed visceral position (situs inversus).

Mixed dextrocardia. The cardiac apex is rightward but the atria and/or ventricles are not reversed. Includes dextrocardia with corrected or ventricular transposition and all forms of dextroversion.

Mixed levocardia. The cardiac apex is leftward but the atria and/or ventricles are reversed. Includes corrected transposition, ventricular transposition, and all forms of levoversion.

Noninverted transposition. See *transposition.*

Physiologically corrected transposition of the great vessels. See *corrected transposition.*

Polysplenia. Fragmentary splenic formation with associated anomalies similar to asplenia except tendency toward bilateral left-sidedness.

Pulmonic ventricle. Ventricle which gives origin to the pulmonary artery. The anatomy of the ventricle and its atrial connection are not identified. Synonym: venous ventricle.

Right atrium (RA). Atrium which receives venae cavae and coronary sinus, has septum secundum, limbus, and fossa ovalis. The right has no spatial significance.

Right ventricle (RV). Ventricle which has tricuspid atrioventricular valve, trabeculae carnae on septal as well as free wall, and multiple small papillary muscles. The right has no spatial significance.

Semilunar valve. Aortic or pulmonic valve.

Sinoatrial inversion. Right atrium on the left and left atrium on the right. Synonym: Situs inversus.

Systemic ventricle. See *aortic ventricle.*

Transposition. Aorta arises from a right ventricle which receives systemic venous blood from the right atrium and pulmonary artery arises from a left ventricle which receives pulmonic venous blood from the left atrium; there is always absence of fibrous continuity between mitral and aortic valves. Synonyms: Complete transposition; noninverted transposition; transposition without ventricular inversion; true transposition. See reference 15 for precise definition and discussion.

Venous ventricle. See *pulmonic ventricle.*

Ventricular inversion. Ventricles interchanged (right atrium to left ventricle and left atrium to right ventricle). It includes corrected transposition and ventricular transposition.

Ventricular transposition. Includes anatomically corrected transposition and isolated ventricular inversion. In isolated ventricular inversion, the whole system distal to atria is transposed. In anatomically corrected transposition, the infundibulum is divided between ventricles. References 14, 15, and 16 are recommended for further discussion of these complicated, rare lesions.

in septation and conotruncal development. Tendency towards bilateral right sidedness. Cardiac position may be unclassifiable. Synonym Ivemark's syndrome.

Atrioventricular valve Valve between atrium and ventricle—belongs to and helps identify ventricle not atrium Tricuspid valve helps identify right ventricle mitral valve helps identify left ventricle

Complete transposition of the great vessels See *transposition*

Concordant In agreement with the normal standard Since the atria are concordant with the noncardiac viscera atrial concordance usually means left atrium on the side of the cardiac apex. Concordant ventricles line up with their traditional atria (right atrium to right ventricle and left atrium to left ventricle) and concordant great vessels line up with their traditional ventricles (right ventricle to pulmonary artery and left ventricle to aorta) The term does not imply anything about situs.

Corrected transposition (physiologically corrected transposition of the great vessels) The great vessels arise from the wrong ventricle but receive blood from the proper atria because the ventricles are also transposed Synonyms incomplete transposition (see definition) inverted transposition transposition with ventricular inversion

Crista supraventricularis Muscle separating atrioventricular valve from semilunar valve Free wall extension (parietal band) belongs to right ventricle. Septal wall extension (septal band) belongs to infundibulum and may be above right or left ventricle. See *ventricular transposition*

D-loop Right ventricle to right or left ventricle The cardiac apex may be anywhere. Synonyms Situs solitus of the ventricles noninverted ventricles

Dextrocardia (1) Mirror image of normal Synonym Situs inversus totalis. (2) Right-sided cardiac apex without the additional implications of the first definition

Dextroposition Rightward displacement of the heart due to extracardiac factors.

Dextrotransposition (d-transposition) The aortic valve is to the right of the pulmonary valve. It usually occurs with d loop in which case same as transposition with situs solitus or corrected transposition with situs inversus.

Dextroversion (1) Right cardiac apex with atrial situs solitus. Synonym Isolated dextrocardia (2) Right cardiac apex with atrial and ventricular situs solitus (see *mixed dextrocardia*)

Discordant (see *concordant*) Opposite to normal standard Discordant atria right atrium on side of cardiac apex. Discordant ventricles left ventricle attached to right atrium Discordant great vessels aorta arising from right ventricle The term does not imply anything about situs.

Great vessel relationships

Solitus	Inversus	
I	IV	Aorta to right of and behind pulmonary artery—normal
II	III	Aorta to right and in front of pulmonary artery—d transposition transposition
III	II	Aorta to left and in front of pulmonary artery—l transposition corrected transposition
IV	I	Aorta to left of and behind pulmonary artery—inversus

Great vessels Aorta (Ao) pulmonary artery (PA) and superior and inferior venae cavae

Heterotaxy Any deviation from the normal visceral positions but usually applied to abdominal deviations other than situs inversus. Synonyms incomplete situs inversus partial situs inversus.

Incomplete transposition (1) Corrected transposition (2) Transposition of one great vessel only double outlet right ventricle for example.

Infundibulum Portion of ventricular outflow tract beginning at crista supraventricularis (see definition) and ending at semilunar valve. Usually right ventricular See *ventricular transposition*

Inverted transposition See corrected transposition

Isolated bulbar inversion Alteration in the spatial relationship of the great vessels

tered 6 ounces of alcohol to 7 alcoholic patients with no clinical evidence of heart disease. No significant changes in myocardial blood flow or ventricular function were observed, and there was no effect on myocardial metabolism. When 12 ounces of alcohol were administered to 11 alcoholic patients the coronary effluent transiently evidenced leakage of cell constituents, despite an increase of coronary blood flow suggesting direct but reversible cardiac injury. The coronary blood flow increment was due to an associated sinus tachycardia rather than direct coronary artery dilatation. A progressive rise in left ventricular end-diastolic pressure and a decrease in the stroke volume were also observed.

Use in angina

Ethyl alcohol has been used in patients with angina pectoris because it presumably can increase coronary blood flow. Many workers have studied the effects of ethyl alcohol on the coronary circulation of healthy anesthetized animals. Conflicting results, especially on cardiac output and coronary flow, have been reported, probably due to the varying condition of each study and the differences in the amount or route of administration of the alcohol given. In a recent study, coronary flow and hemodynamic alterations were measured in dogs, following the intravenous administration of 70 per cent ethyl alcohol at the rate of 0.5 and 1.5 Gm. per kilogram of body weight. One half gram per kilogram of body weight gives a blood alcohol level of about 70 mg. per 100 c.c. which in the human is below the usual legal driving limit of 100 mg. per 100 c.c. This resulted in increased stroke work, increased coronary resistance, and decreased coronary flow. Other workers found with arterial ethanol concentrations of 70 to 120 mg. per cent an increase in left ventricular work and cardiac output and unchanged coronary flow. A third group showed that ethanol blood concentration of 65 to 150 mg. per cent increased coronary flow while mean arterial pressure and coronary resistance decreased.

In man the administration of 15 c.c. of whiskey did not prevent exercise-induced electrocardiographic changes characteristic of ischemia (S-T segment depression and T wave alterations) in patients with angina. A recent study has examined the hemodynamic changes in 8 patients with stable coronary artery disease after a drink of alcohol equivalent to 3 or 4 whiskeys. Observations were made at rest 45 minutes after alcohol intake and following graduated exercise on a bicycle ergometer. Arterial pressure dropped progressively at rest and was lower at each exercise level. The cardiac output fell without a change in heart rate. These hemodynamic events were accompanied by flattening of the T waves in left ventricular leads of the resting electrocardiogram in 2 subjects and with S-T depression in a third. Changes appeared in the exercise electrocardiograms of 2 other patients. The authors concluded that alcohol was acting as a myocardial depressant.

There is laboratory evidence that alcohol diminishes cardiac contractility. In dogs administration of 15 per cent ethanol intravenously at a rate of 0.1 ml. per kilogram per minute for 2 hours causes a progressive decrease in stroke output and a rise in left ventricular end-diastolic pressure. In isolated rat atrium there is an almost linear relationship between alcohol concentration and the decline in myocardial contractility.

Effects on the peripheral vascular bed

Alcohol in moderate doses causes vasodilatation, especially of the cutaneous vessels. One worker, by utilizing digital cutaneous blood flow measurements, has observed that alcohol causes a marked increase in peripheral circulation more effectively than priscol, metacholine chloride, nicotinic acid, or tetraethylammonium chloride. The vasodilatation is most likely the result of central vasomotor depression because the direct action of alcohol on blood vessels is insignificant.

Generalized peripheral arteriolar dilatation may be present in patients with chronic alcoholism. In these patients the cardiac output may be elevated due to arteriolar dilatation acting as multiple arteriovenous shunts. Although hepatic failure was considered a factor in producing this high cardiac output, it has now been demonstrated that a high cardiac output can occur in alcoholic patients with or without liver disease.

Appraisal and reappraisal of cardiac therapy **Edited by Arthur C. DeGraff and Julian Frieden**

Cardiac effects of alcohol

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Ethyl alcohol has been used in the treatment of patients with angina pectoris presumably as a coronary artery dilator but also for its relaxant effects. It also has been used as a cardiac stimulant in other conditions such as trauma drowning and pneumonia. However for many years physicians have known that patients consuming large amounts of alcohol may develop myocardial disease. Recent studies have been performed which cast new light on alcohol s effect on the heart.

Metabolism

Ingested alcohol is normally removed from the body at the rate of 15 to 20 mg per hour The principal site of degradation is the liver Ethyl alcohol is converted to acetaldehyde by alcohol dehydrogenase a zinc-containing metalloenzyme which requires nicotinamide adenine dinucleotide (NAD) as a co-factor In the formation of acetaldehyde NAD is simultaneously converted to the reduced form of nicotinamide adenine dinucleotide (NADH) Acetaldehyde is then oxidized to acetic acid by acetaldehyde dehydrogenase which also requires NAD as a co-factor with further formation of NADH It is not known whether the heart can also directly metabolize alcohol. However the increase in the NADH/NAD ratio in the heart and liver after alcohol administration may produce profound derangements in intermediary metabolism It has recently been demonstrated that alcohol can interfere with the normal oxidative metabolism of serotonin and norepinephrine The increased NADH/NAD ratio may explain the increased triglyceride synthesis and increased lactate production from pyruvate found in the heart and liver

One group of workers administered 6 ounces of vodka to 11 alcoholic patients with no evidence of liver or cardiac disease. A rise in the blood lactate a decline in arterial pyruvate a marked fall in blood glucose a decline in free fatty acids, and a rise in triglycerides occurred one-half hour after the ingestion of alcohol The myocardial extraction of the substrates was consistent with the rise or decline in arterial blood levels with the exception of lactate and glucose the former fell and the latter rose significantly No significant hemodynamic changes were observed

These workers have also demonstrated that patients with chronic alcoholism without clinical hemodynamic or biochemical evidence of heart disease have a consistently negative myocardial balance of isocitric dehydrogenase and malic dehydrogenase This suggests that frequent bouts of acute alcoholism may cause permanent alterations of metabolic pathways or alterations in mitochondrial membrane permeability

Another group of workers also adminis

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stimulant, it is actually a central nervous system depressant. The apparent stimulation is evidenced because of the depressive action of ethanol on the reticular activating system. The inhibitory control mechanisms are depressed and this results in unrestrained activity of many areas of the brain and loss of the integrating control of the cerebral cortex. The action which gives alcohol its value in therapeutics is not its stimulant but its hypnotic action. It is still widely used for this purpose.

Alcohol has been employed by inhalation as an antifoaming agent in the treatment of acute pulmonary edema. Alcohol, by its surface action, can presumably collapse the foam that obstructs the tracheobronchial airways. However, inhaled alcohol has proven to be of limited value in the treatment of pulmonary edema and is therefore not recommended for this use.

Conclusion

Alcohol in large quantity can produce profound metabolic and hemodynamic abnormalities. It is a myocardial depressant and should not be used as a cardiovascular stimulant. There is no evidence that alcohol is useful in treating angina other than as a sedative.

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Long-term cardiac effects of alcohol

Recently hemodynamic studies were performed on a group of alcoholic patients who had no clinical evidence of heart disease and mild to moderate amounts of fatty infiltration without cirrhosis on liver biopsy During the infusion of angiotensin in control subjects there was a progressive rise in stroke output as end-diastolic pressure increments were produced In the alcoholic subjects a greater rise in ventricular diastolic pressure occurred while stroke output failed to increase. This hemodynamic relationship resembles the findings in patients with cardiac disease In an additional study 15 chronic alcoholic patients without clinical cardiac disease and with minimal or no liver disease underwent cardiac catheterization All of the patients had normal resting cardiac pressures. However on exercise 13 of the patients had a significant increase in the left ventricular end-diastolic pressure and mean pulmonary artery pressure.

These studies demonstrate that alcoholic patients without clinical evidence of cardiac disease can exhibit an abnormal ventricular response to exercise or an afterload test. It appears likely that excessive alcohol intake may impair ventricular metabolism and contractility The resultant hemodynamic effects may not be readily discovered in the resting state. The ultimate fate of these cardiac patients without obvious cardiac disease but with hemodynamic abnormalities will be of great theoretical and clinical interest. Presumably some will develop nonobstructive primary myocardial disease. The long term cardiac effect of drinking one to two alcoholic beverages a day are unknown

It appears likely that ethanol is the major pathogenetic factor in many patients with cardiomyopathy Recently a hemodynamic classification has been proposed for primary myocardial disease presumably caused by alcohol At the beginning of the disease or Stage I the cardiac index and cardiac pressures are normal There is a prominent left atrial A wave due to forceful atrial contraction with a resultant presystolic gallop The left ventricular end diastolic volume is normal but the ejection fraction is moderately reduced In Stage II there are two hemodynamic pathways that may be followed In Stage II A type the cardiac index remains normal but the cardiac pressures become elevated in Stage II B type the cardiac index falls and the cardiac pressures remain normal or minimally elevated In both groups, the end-diastolic volume is moderately elevated and the ejection fraction moderately reduced The presystolic gallop and prominent left atrial A waves persist Stage III the late phase of the disease is characterized by a low cardiac index abnormally elevated cardiac pressures greatly increased end-diastolic volume and markedly reduced ejection fraction The presystolic gallop and left atrial A waves persist

Because of the refractoriness of congestive heart failure in the late stages of alcoholic cardiomyopathy a program has been advocated to provide complete bed rest for periods of 6 months to one year At the end of this time 50 per cent of 100 patients with cardiomyopathy demonstrated a reduction in heart size to normal In 25 per cent of patients the heart size was decreased but not to normal whereas in another 25 per cent of patients bed rest was not associated with a significant decrease in heart size During the period of bed rest intake of alcohol was obviously eliminated and digitalis and diuretic therapy were carefully regulated

Light microscopic findings of the myocardium are unimpressive in alcohol cardiomyopathy However two groups of workers have described striking electron microscopic changes mitochondrial swelling fragmentation of cristae swelling of the sarcoplasmic reticulum and varying degrees of myofibrillar disruption Whether these changes are specific for alcohol cardiomyopathy must still be determined

Heavy alcoholic intake may be associated with skeletal as well as with heart muscle disease In acute alcoholic intoxication a syndrome has been described consisting of muscle tenderness myoglobinuria elevated serum creatine phosphokinase levels and poor lactic acid response to ischemic exercise The acute myopathy may progress to a chronic form with proximal and diffuse muscle atrophy and weakness Abstinence from drinking is associated with clinical improvement

In spite of the long use of alcohol as a

stimulant it is actually a central nervous system depressant. The apparent stimulation is evidenced because of the depressive action of ethanol on the reticular-activating system. The inhibitory control mechanisms are depressed and thus results in unrestrained activity of many areas of the brain and loss of the integrating control of the cerebral cortex. The action which gives alcohol its value in therapeutics is not its stimulant but its hypnotic action. It is still widely used for this purpose.

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Diffuse glomerulonephritis associated with infected ventriculoatrial shunt

Black and his co-workers,[1] in 1965 reported two cases of the nephrotic syndrome associated with an infected atrioventricular shunt, and eight additional cases have been reported since.[1-4] We have observed six children each of whom had diffuse glomerulonephritis and an infected ventriculoatrial shunt.

The interval between the shunt operation (done because of hydrocephalus) and the diagnosis of renal disease varied from 1 to 74 months. Evidence of septicemia preceded the appearance of renal disease in five of the six children.

Four children had features of the nephrotic syndrome, as characterized by edema and proteinuria. Hypoproteinuria and hypercholesterolemia were present in each of the three children in whom these determinations were done. All six children had hematuria and elevated level of blood urea or blood urea nitrogen. All had anemia, and five of the six had hepatosplenomegaly. Three were hypertensive, and all had cylindruria. Red cell casts were present in the urine of four children, white cell casts in the urine of five, and hyaline and granular casts in the urine of four.

In each child a microorganism was cultured from the blood or shunt material after removal of the shunt. The infecting organism was coagulase-negative staphylococcus in five instances, and coagulase-positive *Staphylococcus aureus* in one instance.

After removal of the shunt, renal function improved and edema and urinary abnormalities decreased. Three patients died but death appeared to be related to disease of the central nervous system.

Biopsy material from two patients showed generalized, diffuse proliferation and swelling of the endothelial and mesangial cells. Early crescent formation was observed in several glomeruli. Polymorphonuclear leukocytes were present in the capillaries, and in some areas there was necrosis of the capillary wall. Thrombi were not present. The findings were consistent with acute and early subacute proliferative glomerulonephritis. No organisms were seen on Gram stain.

Immunofluorescent staining of renal tissue obtained in one case revealed deposits of IgM globulin in the glomeruli and some in lobular distribution in the glomeruli and some IgG globulin and β complement in a similar distribution. No deposition of albumin or IgA globulin was detected and focal fluorescence for fibrin was noted primarily in Bowman's space.

Since renal disease has not been produced in laboratory animals infected with coagulase-negative staphylococcus there is no proof of a causal relationship between the diffuse renal disease and staphylococcal bacteremia. However this circumstance has now occurred in sufficient numbers to make it unlikely that the association is due to chance.

Although direct bacterial embolization of the kidney or the production of a microangiopathy represents possible pathogenic mechanisms, it seems more likely that an immunologic response to infection is the cause of the renal disease. This assumption is supported by the finding of a low complement level in one of our patients and in the patients reported on by Holland by Northway and associates, and by Piel. Furthermore Black and co-workers found IgG globulin and complement in the affected glomeruli and in our series, in the only patient studied, IgM globulin, IgG globulin, and complement were found in the glomeruli. Until the disease can be reproduced in the experimental animal the association of coagulase-negative bacteremia and diffuse renal disease as well as the pathogenesis of renal disease in these patients, will remain uncertain.

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Ethacrynic acid: Its usefulness and untoward effects

Ethacrynic acid, an unsaturated ketone derivative of phenoxyacetic acid, proved to be extremely effective in the treatment of various edema states.[1-4] The potent diuretic effect has been ascribed to its ability to bind sulfhydryl groups of renal cellular proteins, resulting in inhibition of renal tubular sodium reabsorption. The primary site of action is in the ascending loop of Henle as well as the proximal convolution of the renal tubule. Thus there is marked interference with the urinary hydrogen excretion.

A profound diuresis may be seen in patients resistant to other diuretic agents, and, in general, the properties of ethacrynic acid are similar to those of furosemide.

The unique properties of ethacrynic acid insure its usefulness in a wide range of clinical situations. *The rapid onset of action following intravenous* administration[illegible] has been utilized effectively in the treatment of acute pulmonary edema.[illegible] It has also been proved to be invaluable in patients with intractable heart failure[illegible] and other forms of resistant edema. In addition, it has been used with success in patients with chronic renal failure[illegible] and acute renal failure. In acute renal failure, preferential renal cortical ischemia has been demonstrated, and, as it has been shown that ethacrynic acid increases cortical blood flow in the dog during diuresis, it is possible that this is its main mode of action in provoking diuresis.

With increasing use of ethacrynic acid, numerous adverse effects have been recorded. The more serious ones include agranulocytosis,[illegible] acute pancreatitis,[17] and hepatocellular damage.[illegible] Other side effects include cholestatic jaundice and symptomatic hypoglycemia, and contraction of extracellular fluid volume with hypotension and collapse. Hypochloremic alkalosis, hypokalemia, and hyperuricemia may follow continued use of the drug.

An unusual side effect has been the development of acute transient deafness following intravenous use described first by Maher and Schreiner. Subsequently Schneider and Becker[illegible] reported this complication in five cases following oral and intravenous administration. Schmidt and Friedman[17] described one case after oral use of the drug.

We have recently reported 5 cases of deafness following oral and intravenous administration.[illegible] In 3 patients the deafness was permanent. Of the 12 patients reported to date with deafness, 10 were azotemic; one had normal renal function, and, in the other, renal function was not mentioned. The ages in 11 patients ranged from 20 to 76 years. There were 3 males and 8 females. Other associated side effects in these patients were tinnitus in 3, fullness in the ear in 2, and one each with earache, dizziness, vertigo, and nystagmus. Maher and Schreiner[4] described vertigo alone in one of their patients. In addition, we have observed an acute organic brain syndrome in 2 patients, probably associated with acute deafness. Both developed a peculiar psychosis within 15 minutes after intravenous injection of ethacrynic acid. This consisted of hallucinations, inappropriate behavior, and maniacal manifestations. The symptoms persisted for about 30 minutes and were reproduced in both patients when the drug was again administered. The psychosis could be due to the superimposition of deafness in a patient with preexisting cerebral impairment, resulting from uremia and electrolyte imbalance, or it might be the effect of acute electrolyte changes within the brain, or a combination of these factors.

The cause of the deafness following ethacrynic acid is not known. Symptoms reflecting disturbances on the vestibular apparatus and cochlea suggest alteration in electrolyte concentration or acid-base balance in these organs. However, the lack of similar symptoms following the use of other diuretic agents speaks against this possibility. Moreover, the development of permanent deafness in 4 patients is not in keeping with this hypothesis. The proclivity of ethacrynic acid to bind sulfhydryl groups is probably not significant, as organic mercurials act by the same mechanism without producing these symptoms. However, mercurials do not act on the distal tubular cells as does ethacrynic acid, and it is possible that similar selectivity of action may occur with ethacrynic acid in the cochlea and vestibular apparatus. As the majority of patients were azotemic, it is also possible that ethacrynic acid or its congeners formed toxic complexes by combining with organic compounds retained in azotemic patients. Schneider and Becker suggested that retention of cysteine adduct of ethacrynic acid in azotemic patients may be the cause of hearing loss.

Hearing loss was unrelated to the route of administration or dosage used. There was also no correlation between the onset of hearing loss and the use of ethacrynic acid. As this complication was more liable to occur in patients with renal insufficiency we suggest that ethacrynic acid be used with caution

in such patients. If the patient proves to be resistant to conventional diuretic agents, furosemide may be preferable. If ethacrynic acid is used, the patient should be observed closely for cochlear and vestibular symptoms and serial audiogram should be done before and during treatment. The emergence of symptoms or changes in the audiograms are indications for withdrawal of the drug.

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A new coronary prognostic index

During the last few years, a number of new forms of treatment have been claimed to reduce the hospital mortality rate from acute myocardial infarction. Foremost among these has been the treatment of ventricular fibrillation, with the subsequent development of coronary care units[1-4] and the prophylactic treatment of warning ventricular arrhythmias. In addition, it has been claimed that hyperbaric oxygen, sedation, and low molecular weight dextran infusion lower the mortality rate in this condition. Any treatment which can lower the death rate from this common disease is worth-

hile, but to establish marginal benefit it is necessary to study large number of patients and to balance treated and control groups according to the severity of their disease. For instance, although it is undeniable that patients resuscitated from ventricular fibrillation represent an improvement in the mortality rate from infarction, the 14 to 17 per cent death rate reported from coronary care units[1-4] must be compared with the wide range of deaths, from 15 to 40 per cent, reported before the establishment of these units.[5-10] It is probable that the main factors contributing to this wide ariation in earlier reports were the definition of infarction used, the type of patients referred to the investigating hospital, and the age structure of the population.

If comparisons of mortality figures from acute infarction are to have any meaning, they must be standardized according to the severity of the infarct. For this reason Peel and associates[13] and Hughes and co-workers[14] formulated coronary prognostic indices (C.P.I.) by adding weightings given to adverse clinical features, determined retrospectively from the patient records, so that the higher the index the greater was the chance of death. The index which has been recently described[15] is considered to be based on more objective criteria than the earlier indices and is compiled from material collected prospectively so that bias is reduced as far as possible.

The C.P.I. was constructed from group of 757 patients investigated prospectively in connection with trial of propranolol[16] with which was combined with study on the hospital mortality rate following infarction.[17] The patients were all those admitted to the three public hospitals in Auckland, New Zealand, over one year who had acute infarction, defined by the fulfillment of t least two of the following criteria (1) characteristic clinical presentation, (2) Q waves, S-T elevation, or T-wave inversion in the electrocardiogram (ECG) with evolutionary changes, (3) a rise in serum glutamic oxaloacetic transaminase to over 40 U per milliliter on one of three successive days. These patients received normal hospital care, but did not have routine antiarrhythmic treatment or electrocardiographic monitoring, which was not available at the time.

Data which was considered to be relevant to prognosis was collected in numerical form immediately after admission, and transferred to IBM punch cards. From preliminary examination of the data, it as found that six factors could be best related to hospital survival. These factors ere age,

Table I. Weightings fo the six factors selected for constructing the C.P.I.

Factor	X	Y
Age (y) (X Y)		
<50	0.2	
50–59	0.4	
60–69	0.6	3.9
70–79	0.8	
80–89	1.0	
Position of infarct (X_4, Y)		
Anterior transmural	1.0	
Left bundle branch block	1.0	
Posterior transmural	0.7	2.8
Anterior subendocardial	0.3	
Posterior subendocardial	0.3	
Admission systolic blood pressure (mm. Hg) (X Y)		
< 55	1.0	
55–64	0.7	
65–74	0.6	
75–84	0.5	
85–94	0.4	10.0
95–104	0.3	
105–114	0.2	
115–124	0.1	
>125	0	
Heart size (X Y)		
Normal	0	
Doubtfully enlarged	0.5	1.5
Definitely enlarged	1.0	
Lung fields (X Y)		
Normal	0	
Venous congestion	0.3	
Interstitial edema	0.6	3.3
Pulmonary edema	1.0	
Previous ischemia (X Y)		
No ischemia	0	
Previous angina or infarction	1	0.4

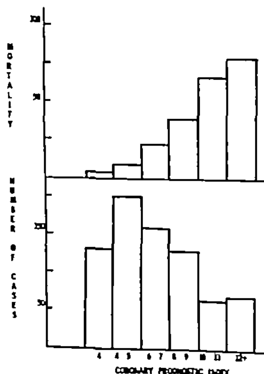


Fig. 1.

in such patients. If the patient proves to be resistant to conventional diuretic agents, furosemide may be preferable. If ethacrynic acid is used the patient should be observed closely for cochlear and vestibular symptoms and serial audiograms should be done before and during treatment. The emergence of symptoms or changes in the audiograms are indications for withdrawal of the drug

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A new coronary prognostic index

During the last few years, a number of new forms of treatment have been claimed to reduce the hospital mortality rate from acute myocardial infarction. Foremost among these has been the treatment of ventricular fibrillation, with the subsequent development of coronary care units [1-4] and the prophylactic treatment of warning ventricular arrhythmias In addition, it has been claimed that hyperbaric oxygen, sedation, and low molecular weight dextran infusion lower the mortality rate in this condition. Any treatment which can lower the death rate from this common disease is worth

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Pulses—Visible and palpable

The medical student and physician in training frequently has difficulty palpating the ankle and popliteal pulses. Experienced clinicians may also find palpation limiting as evidenced by significant observer variability. We have noted that the posterior tibial and popliteal pulses are frequently visible as well as palpable. A study was undertaken to evaluate the efficacy of visual examination of the posterior tibial and popliteal pulses.

One hundred men and 100 women were examined. The subjects examined were ambulatory patients (with the exception of 35 female hospital employees).

The age range for the entire group was 14 to 84 years with an average of 43 years. The age range for the male group was 20 to 76 years with an average of 50 years and the female age range was 14 to 84 years with an average of 35 years. The primary diagnosis or the presence or absence of peripheral vascular disease was not known prior to examination.

Each subject was examined with tangential light from a penlight* to determine if the posterior tibial and popliteal pulses were visible. Palpation was then performed. The posterior tibial pulses were examined with the patient supine. Adduction of the foot was occasionally helpful in locating or accentuating a visible pulse. The popliteal pulses were examined with the subject prone and the leg passively flexed at 45 to 90 degrees and held relaxed in the examiner's hand, leaving the other hand for the direction of the light.

The results are shown in Table I. Excluding subjects with peripheral edema (12 women, 5 men), 93 per cent of palpable posterior tibial pulses and 92 per cent of palpable popliteal pulses were seen in males. The corresponding results in females were 50 and 40 per cent.

The examination of peripheral pulses is important in the evaluation of peripheral vascular disease, arterial emboli, and heart disease. Palpation is the accepted mode of examination of pulses and to our knowledge, a study utilizing visualization of peripheral pulses has not been done. Excluding edema, over 90 per cent of the posterior tibial and popliteal pulses palpable in males were visible. The lower yield of visible pulses in females is probably due to the presence of more subcutaneous fat and less atherosclerosis than in males. The proportion of visible to palpable pulses in both males and females appears to increase with age as subcutaneous fat decreases and atherosclerosis increases. In every instance, a visible pulse was also palpable.

Visualization of posterior tibial and popliteal pulses adds a new dimension to the examination of these arteries. These pulses should *not* be recorded as absent unless they are neither seen nor felt. Visualization should be especially helpful to the examiner who has difficulty locating these pulses and distinguishing the patient's pulse from his own.

Finally, a visible pulse is often easily seen simul-

Table I. Results of examination of posterior tibial and popliteal pulses by vision and palpation in 100 male and 100 female subjects

Posterior tibial			*Popliteal*		
% visible	*% palpable*	*% not detected*	*% visible*	*% palpable*	*% not detected*
Males (ages 20-76)					
84	93	7	88	97	3
Females (ages 14-84)					
45	94	6	40	99	1

*Robb-Allen Prints, compliments of Wyeth Pharmaceuticals, Philadelphia, Pa.

systolic blood pressure on admission to hospital heart size and degree of congestion of the lung fields on a chest x-ray taken as soon as possible after admission, the position and degree of infarction assessed from a 12 lead ECG and the history of previous ischemia. Factors not related to survival were sex, the time between the onset of infarction and admission to hospital, previous diabetes, hypertension, and obesity. Each factor associated with survival was then given a numerical weighting between 0 and 1, the weighting being proportional to the effect on mortality which was encountered. These weightings were then substituted for the factors in each patient, and by the method of discriminant analysis, numbers (designated Y) were found which when multiplied by the weightings (designated X) gave the final weighting for the construction of the index. The more serious the prognostic factor under consideration, the higher the value for Y. The C.P.I. was thus the sum $X_1Y_1 + X_2Y_2 + \ldots X_nY_n$. Y values and the C.P.I. for each patient were calculated by computer. The weightings (X and Y) are shown in Table I. All 757 patients were then separated into six groups according to their C.P.I. and a stepwise increase in the mortality rate was found, ranging from 3 per cent where the index was less than 4 to 78 per cent where it was 12 or more (Fig. 1).

The index was next applied to a group of 300 patients monitored in a coronary care unit which was opened immediately after this study was completed. The same data were recorded in these patients, and assessed by two of the same observers. Using the index, the patients were divided into three groups of mild, moderate, and severe infarction; the respective hospital death rates for the patients who did not have intensive care or resuscitation were 5, 31, and 72 per cent. The respective percentage mortality rates of patients treated in the coronary care unit were 7, 12, and 68 per cent. Thus, the mortality rate was reduced from 31 to 12 per cent ($\chi^2 = 13.4$, $p < .001$) in the group of moderate severity but was unchanged in the mild and severe cases. This moderate group comprised about a third of the total patients.

Results from the coronary care unit were then compared with those from the same hospital during the year before the unit opened. This hospital was one of the three contributing to the original study and during the year under consideration an effective resuscitation service in the general wards had resulted in the successful treatment of ventricular fibrillation in six cases. When allowance was made for this fact, there was no significant difference in the mortality rate between patients treated in the unit and those treated in the general wards. Although these results indicate that coronary intensive care can be practiced successfully outside a special unit, it is considered unlikely that good results can be consistently achieved without centralized monitoring and resuscitative facilities.

The findings with regard to the relative importance of the prognostic factors studied were mainly in agreement with those of previous workers. These factors have now been given a logically derived numerical weighting, however, and it is thought that the resulting index should form a valuable measure for assessing new forms of treatment for acute myocardial infarction.

R. M. Norris, M.D., M.R.C.P., M.R.A.C.P.
P. W. T. Brandt, M.B., M.C.R.A., F.F.R.
D. E. Caughey, M.B., M.R.C.P.E., M.R.A.C.P.
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The results are shown in Table 1. Excluding subjects with peripheral edema (12 women, 5 men), 95 per cent of palpable posterior tibial pulses and 92 per cent of palpable popliteal pulses were seen in males. The corresponding results in females were 50 and 40 per cent.

The examination of peripheral pulses is important in the evaluation of peripheral vascular disease, arterial emboli, and heart disease. Palpation is the

*Welch-Allyn Penlite, compliments of Wyeth Pharmaceuticals, Philadelphia, Pa.

Table 1. Results of examination of posterior tibial and popliteal pulses by vision and palpation in 100 male and 100 female subjects

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Visualization of posterior tibial and popliteal pulses adds a new dimension to the *examination* of these arteries. These pulses should not be recorded as absent unless they are neither seen nor felt. Visualization should be especially helpful to the examiner who has difficulty locating these pulses and distinguishing the patient's pulse from his own.

Finally, the visible pulse is often easily seen simul-

taneously by several observers, virtually eliminating controversy regarding its presence.

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Letter to the Editor

Thermodilution flowmeter

T the Editor

In the article entitled Pulsatile aspects of coronary sinus blood flow in closed-chest dogs by Stein and associates (AMER. HEART J 78:331 1969) reference is made to the thermodilution flowmeter described by me in the *Journal of Applied Physiology* (21:1883 1966) It needs to be pointed out that this is not thermistor *decity* probe as mentioned by Doctor Stein. It is rather catheter flowmeter hich measures mean *volume* flow in the coronary sinus, based on the principle that heat produced by an electrical coil is uniformly distributed in the blood stream through the mechanical action of stirrer nd that the temperature change obtained, which is measured downstream, is inversely proportional to flow I this regard, I find Dr Stein statement, thermistor transducer was also utilized by Afonso for the measurement of coronary sinus elocity to be incorrect and misleading

Needless to say measurements of flow nd phasic variations in flow ith elocity flow probe, ithout simultaneous measurements of the essel diameter do not permit meaningful interpretation

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Reply

T the Editor

Thank you for forwarding Dr Afonso letter to me Dr Afonso is certainly correct regarding the capabilities of his thermodilution catheter-tip flow meter

I do not completely agree th Dr Afonso comments regarding the interpretation of coronary sinus elocity I an article now in press in the AMERICAN HEAR JOURNAL, showed linear relationship bet een increments of coronary sinus elocity and increments of left anterior descending coronary flow in dogs after several interventions. Therefore, it may in fact, be possible to obtain some meaningful interpretation from the measurement of coronary sinus velocity ithout simultaneous measurement of the vessel diameter Of course, more precise information ould be obtained from total flow measurements

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Muffling the information explosion by throttling self-serving advertisers

T the Editor

Medical research has become incredibly productiv in recent years, and for the plethora of articles, lectures, nd seminars on these new discoveries all of us can be truly gr teful. Unfortunately much of the so-called information explosion ha a different and less lofty origin. The publish-or perish philosophy of our universities nd research Institutes has caused to be published ast array of trivia and poorly performed studies. About this, much has been said but little accomplished. At least, though, the problem is recognized as such. However there is yet another sourc of surfeit which, pparently is held so sacrosanct that it has not even been recognized as an excess, and yet it is about this that w should most raise our voices in anger

Year after year some of the best know figures in Medicine regularly inundat the scientific journals ith a monotonous repetition of the same hackneyed ideas, hile others seem to be bent on an endless cycle of travels to medical meetings where they re-re-represent their effet theses ad nauseum. For example, if I read one more article on the two-step electrocardiogram by You-Know Who, or hear one more lecture on anticoagulant ther py by You-Know Who-Also—I think I shall scream! Surely repetition carried out t such extremes cannot be justified on the basis of education. Rather the objec tiv clearly seems t be that of keeping the authors names constantly before the medical community i order to maintain their high positions i the ni ersities, hospitals, and scientific societies Undoubtedly they believe, as do the soap and toothpaste manufacturers, that constant repetition of lie ill transform it into truth.

Who is to blame for such self-serving ad ertising? (And there is no better w y t describe this reprehensible beha ior than that.) Certainly the individuals involved must assume their share of the guilt, but, in my opinion, the journal editors and conference chairmen are the mai culprits. It is their privilege nd duty to select fresh, worth hile topics for presentation to their udiences, and their abd cation of this responsibility hen confronted by request for time or space from patrician provides the forum for these self-seeking advertisers to tout their sales pitches. The result is that valuable journal space or conference time is wasted, that the audience is caused to groan "Oh no, not again!" and that sincere young men become prematurely cynical about the behavior of those whom they would like to emulate.

I for one, have had my fill. Henceforth, I expect to hold every editor or conference chairman strictly accountable for his censorship responsibility Abuses will be publicly challenged.

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Circulation Research. These t monographs are additional good ones. The clinical trial with unsaturated fats showed that a decrease in cholesterol promptly followed dieting. A lowering of the incidence of major coronary cardiac events on unsaturated diets as not convincing from the data presented. Young people seemed to benefit more from the unsaturated f ts than old people. The monograph is orth careful review by all physicians because of the emphasis and claims of the alue of unsaturated fats in the prevention of therosclerosis.

The monograph on myocardial hyperfunction, hypertrophy and heart failure consists of review of ideas, theories, and studies from the Soviet Union. Those ho are interested in the work in the U.S.S.R. will find this report useful. In general, the concepts there are essentially the same as in the United States.

BRITISH MEDICAL BULLETIN MECHANISM OF TOXICITY Scientific Editor W M Aldridge, Vol. 25 No. 3, September 1969 Medical Department, London, 1969 The British Council. Price $6.50.

The British Medical Bulletin continues to publish excellent and timely issues. This one on the mechanism of toxicity is another such timely publication—seventeen papers are included covering such subjects as biochemical lesions, reversible binding of toxic compounds to macromolecules, delayed neurotoxic action of some organophosphorus compounds, nitroso compounds, metabolism of toxic substances, diet and toxicity toxic activity of microbes, and others. The various presentations are relatively short but are ritten clearly and well. With man living in toxic orld due to extensive use of drugs, insecticides, and food preparations, and water and air pollution, this issue should be of interest to all physicians as well as pharmacologists and chemists of all fields. This is another good issue of the Bulletin and is highly recommended.

CARDIAC ARREST AND RESUSCITATION Third Edition. By Hugh E. Stephenson, J A.B., B.S M.D F.A.C.S., St. Louis, 1969 The C. V Mosby Company 659 pages Price $29.50.

The third edition of this book tests to its usefulness and popularity The book, written by many contributors, includes discussions of history mechanisms, recognition, techniques of resuscitation, complications, incidence, prognosis, and other aspects of the subject. The book is lucid and ell illustrated. New ideas, techniques, drugs, and experiences are included. Everyone who is engaged in medical and paramedical endeavors concerned with patient care ill find this book to be useful. Sudden death can occur under any circumstances. T have it occur in the presence of physician ho is not acquainted ith the essentials of cardiac resuscitation is not only unfortunate for the patient but extremely embarrassing to the physician. It must be remembered that no book can replace experience. Those who wish to learn cardiac resuscitation will find training period in coronary care nit supported by this book to be extremely profitable. This book is highly recommended. The author will find the use of cardiologists who ork daily in coronary care units to be very careful contributors for his next edition.

KLINISCHE VEKTOR-ELEKTRO KARDIOGRAPHIE. By Paul Lichtlen, Berlin, 1969 Springer Verlag, 233 pages.

This monograph describes the clinical pplications of vectorcardiography. Lichtlen clearly presents the theory of vectorcardiography for the clinician. The illustrations of actual ectorcardiograms are excellent. The diagrams used to explain theories and concepts are simple and well related. The author describes in few pages the main spatial ectorcardiographic manifestations of the common forms of heart disease. The Frank system is used in his studies, although he fails to indicate hy he employed this relati ely complex system. He does not indicate the difficulties the system offers in newborn infants, obese patients ith large breasts, or patients w th deformed chests. Nevertheless, this is valuable monograph which also contains good bibliography

CARDIAC ROENTGENOLOGY Plain Films and Angiocardiographic Findings. By William T Meszaros, M.D F.A.C.R., American Lecture Series, Springfield, Ill., 1969 Charles C Thomas, Publishers, 586 pages. Price $38.00.

The physicians hose time and funds are limited for books ill onder if this monograph adds anything especially new to the many already ailable on the subject. The monograph presents the problems of cardiac roentgenology in the conventional fashion. It is divided, for example, into three parts, iz., general considerations, *acquired heart diseases, and congenital heart diseases.* Technique, normal standards, photographs of chest films, angiocardiograms, etc., are presented. Many of the illustrations are "fuzzy whereas others are quite sharp and clear The text is satisfactory but not outstanding. The bibliographies are good. The monograph is recommended to those who may not ha a book on the subject already

VASCULAR INSUFFICIENCY Mechanism and Management Edited by John R. Kelsey J M.D and Earl F Beard, M.D Springfield, Ill., 1969 Charles C Thomas, Publisher 242 pages. Price $10.75.

This monograph (publication No. 738 of the American Lecture Series) on vascular insufficiency is compendium of papers by thirteen contributors from Baylor University Medical College. The main thesis is concerned with mechanism and management. The contributions are too brief and considerably incomplete. For example, Chapter 1 on the pathogenesis of atherosclerosis

Book reviews

INTRODUCTION TO ELECTROCARDIOGRAPHY. By J. Willis Hurst, M.D., and Robert Myerburg, M.D. New York, 1968, McGraw-Hill Book Company, Inc. 314 pages.

This small book is presented in two major parts. Part One deals almost exclusively with spatial vector electrocardiography or the vector concept, for the interpretation of electrical activity of the ventricular myocardium. Although spatial vectorial concepts for display and analysis of the electrical activity of the heart have been known for years and are paramount in the understanding and teaching of electrocardiography, the approach presented in this book is that orientation originally expounded by Dr. Robert Grant. This approach enjoyed some popularity and in several institutions became the foundation for teaching electrocardiography. It should be noted, however, that this method is inexact and artificial and this reviewer has never been convinced of its value or uniqueness in electrocardiography. Under this method one sees such descriptions of an electrocardiogram as:

"(A) The frontal plane projection of the mean QRS, T and terminal 0.04 vectors. The terminal 0.04 portion of the QRS complex is markedly negative in Lead I and isoelectric in Lead aVf. The mean vector representing this portion of the QRS complex would be directed perpendicular to Lead aVf and toward the negative pole of Lead I.

(B) The terminal 0.04 vector is rotated 30° anteriorly because this portion of the QRS complexes is positive in V and V and negative in V_4, V_5, V_6.

(C) The mean QRS vector is rotated 30° anteriorly because the transitional pathway passes between electrode positions V and V. In such a case V, V_2, V will record resultantly positive deflections and V_4, V_5, V will record resultantly negative deflections.

(D) The mean T vector is rotated 15° posteriorly because the transitional pathway for the T wave is located between electrode positions V and V_3.

(E) Summary. The QRS duration is 0.12 second. The terminal 0.04 vector is directed to the right and anteriorly."

The above seems unnecessarily excessive in describing an electrocardiogram with right bundle branch block, particularly when the potential significance of leftward deviation of the initial portions of the QRS loop is not mentioned relative to the tracing in question.

In observing individuals trained to interpret electrocardiograms by the method alluded to above, this reviewer has been impressed at the lengthy descriptions given to the "direction" or rotation of the initial 0.04 vector, the terminal 0.04 vector, the mean T vector, and the like only to end with an equivocal diagnosis in terms of clinical application or prediction of anatomical abnormalities likely to be substantiated at autopsy.

Part Two of this book by Hurst and Myerburg deals with the presentation of the cardiac arrhythmias through use of the A-V diagram. As noted by the authors this approach represents nothing unique and has been in standard use by many electrocardiographers since the days of Sir Thomas Lewis.

Although written with simplicity, this reviewer found the format of the book difficult to handle. Because of text descriptions of electrocardiograms displayed on other pages throughout the book, and references to figures by numbers rather than by pages, the reader wastes time flipping through pages searching for appropriate figures. By and large, however, the figures as presented are clear, simple, and of good quality. The references provided at the end of the book are brief and highly selective and a number of important works representing milestones in the development of understanding and teaching of electrocardiographic principles and practical applications are disregarded.

It is difficult to know what category of readers would derive value from this small book. The fundamentals as presented herein are available in previous publications by Grant and co-workers. As indicated, this reviewer is not convinced that their methods are superior to others either in understanding or teaching electrocardiography to beginners. For experienced electrocardiographers little of value can be gained from this work. The real problems as encountered in day-to-day interpretation of electrocardiograms have largely been avoided.

A CONTROLLED CLINICAL TRIAL OF A DIET HIGH IN UNSATURATED FAT. I. Preventing Complications of Atherosclerosis. American Heart Association Monograph No. 25. By Seymour Dayton, M.D., Morton Lee Pearce, M.D., Sam Hashimoto, M.S., Wilfrid J. Dixon, Ph.D., and Uwamie Tomiyasu, M.D. New York, 1969, American Heart Association, 63 pages. Price $4.00.

THE MYOCARDIUM IN HYPERFUNCTION, HYPERTROPHY AND HEART FAILURE. American Heart Association Monograph No. 26. By Felix Z. Meerson, M.D. New York, 1969, American Heart Association, 161 pages. Price $4.00.

The American Heart Association has been publishing a series of monographs on many important aspects of cardiology and the circulation. They all appear as special supplements of Circulation and

ENCYCLOPEDIA OF MEDICAL RADIOLOGY—VOL. 10, NO. 1—ROENTGEN DIAGNOSIS OF THE HEART AND BLOOD VESSELS. Edited by L. Diethelm, O. Olsson, F Strand, H. Vieten, and A. Zuppinger New York, 1969 Springer Verlag, 789 pages. Price $74 00.

MANAGEMENT OF MEDICAL EMERGENCIES, ed. 2 Edited by John C. Sharpe and Frederick Marx, Jr New York, 1969 McGraw Hill Book Company Inc., 756 pages. Price $19.50.

MODERN TREATMENT—Vol. 6, No. 4 July 1969—Psychiatry in Medical Practice. By Ephraim T Lisansky and Bernard R. Schochet, New York, 1969 Paul B. Hoeber Medical Division, Harper & Row Publishers. Pages: 1,500 per year Price $16 00 per year

THE PREVENTION OF CORONARY HEART DISEASE. By R. Mulcahy and N Hickey Dublin, 1969 Irish Heart Foundation, 66 pages.

SILENT VICTORY By Carmen McBride, Chicago, 1969 Nelson-Hall Co., 221 pages. Price $5 95.

BIOCHEMICAL AND CLINICAL ASPECTS OF ALCOHOL METABOLISM. By V M Sardesai, Springfield, Ill., 1969, Charles C Thomas, Publisher 319 pages. Price $27 00.

COOK TO YOUR HEART CONTENT ON LOW-FAT LOW-SALT DIET. By Daniel Liebowitz, W Jann Brown and Marlene Olness, Menlo Park, Calif., 1969 Pacific Coast Publishers, 150 pages. Price $4.95

THE DIAGNOSIS OF BLEEDING DISORDERS. By Charles A. Owen, E. J Walter Bowie, Paul Didisheim, and John H. Thompson, Jr Boston, 1969 Little, Brown & Company 300 pages. Price $15.00.

DISEASES OF THE CHEST By H. Corwin Hinshaw Philadelphia, 1969 W B. Saunders Company 799 pages. Price $25 00.

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is limited to 8 pages. This may be justified since the pathogenesis is unknown. Nevertheless, such factors as age, race, sex, etc., are not discussed. Practically nothing is said about the medical management of arterial insufficiency whereas a whole chapter is devoted to surgical management. The authors fail to emphasize the importance and value of early diagnosis, prevention, and role of medical management of peripheral arterial disease and the use of surgery in conjunction with medical procedures. Likewise they fail to indicate the difficulties and poor results of surgical care. This book does not present the problems of mechanisms and management of vascular insufficiency accurately or adequately. Pathologic physiology is practically absent. Unless a job is well done it may be better not to do it at all.

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American Heart Journal

April 1970 Volume 79 Number 4

Editorial

Performance of the computer and physician in the analysis of the electrocardiogram

C. A. Caceres, M.D.
H. M. Hochberg, M.D.
Washington, D. C.

Computer analysis of the electrocardiogram is an accomplished fact. The pertinent question in the minds of most physicians is the "accuracy" of the analyses. The problem is defining "accuracy" and the best method to evaluate it. Studies dealing with accuracy have used physician-readers as the standard of reference. These studies show that a physician's reproducibility of judgment is approximately 80 per cent if he is a trained electrocardiographer. The generalist's reproducibility is probably less. Since the physician's variability in judgment affects the results, is this a valid method of evaluating the performance of a machine system?

The precision of the individual computer wave-form measurement is as adequate as painstaking calculation by laboratory physicians, as shown by Dobrow and associates. A sustained level of measurement accuracy possible by computers is not often achieved by physicians. Similarly, once programmed to repeat interrelation of measurements in a set of criteria, the computer is far more reliable than man, as the machine system always follows designated logic without subjectivity.

In the development of any machine system the standard must be orders of magnitude more precise and accurate than the proposed machine system. When the system exceeds the standard, as it does in the case of computers and physicians, new standards or methods of evaluation must be used. Otherwise judgment of system performance remains subjective and will vary far more than the system itself.

To evaluate a machine system, the input must be compared with the output with reference to prescribed logic. In the ECG-computer system, the measured wave forms should lead to diagnoses according to criteria. If indeed they do, then the machine is functioning as it should. However, electrocardiographers' criteria are currently

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**Formerly, Chief, Medical Development Unit, MSDL; Research Instructor, George Washington University School of Medicine, Washington, D. C.

Announcements

A Day of Cardiac Pathology with Jesse E. Edwards M.D., March 19 1970 will be presented by the University of Florida College of Medicine, Departments of Medicine, Pediatrics, Surgery and Cardiac Radiology Gainesville, Fla. and the Regional Medical Program for North Florida, co-sponsored by the Florida Heart Association, Alachua County Division.

For additional information write to the Division of Postgraduate Education, J Hillis Miller Health Center Box 758, Gainesville, Fla. 32601

The Seventh Congress of the European Dialysis and Transplant Association will be held in Barcelona Spain, on June 25 to 27 1970. This Congress will also include a scientific and commercial exhibition.

Information may be obtained from the Secretary of the Congress, Instituto Policlinico, Platon 21, Barcelona Spain.

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based on a combination of experience limited for an individual cardiographer Even the literature as a whole is based on small numbers. With this mode of analysis electrocardiographic criteria would have to remain subjective and variable.

The performance of a machine can be defined on the basis of the number of correct functionings, that is correct statements, over the total number of statements made. In the ECG-computer system if the measurements are made incorrectly or the criteria program operates incorrectly the direction of action to be taken is clear—that is, go back to the computer programmer and ask that he clarify the logic given the computer If the system performs as it should in measurement and in logic but still disagrees with the physician we must ask ourselves, What interpretation should be made? Should other measurements have been looked at? In other words we have a physician not a computer problem

The fact of the matter is that computer cardiogram programs today have minimal measurement error in contrast to human readers. Further they consistently follow the diagnostic logic they were given yet there still may be disagreement between computer and physician.

To help us gain a further understanding of why we may disagree with computer output, we can consider as an illustration of what has been discussed the evolution of improvement in computer performance in a functioning heart station

Two hundred ninety three computer processed electrocardiographic tracings comprising the total sample from one month at one test hospital were reviewed A tabulation of the results is made in Table I

Table I *Analysis of 293 ECG's submitted for computer processing**

Analysis		*No*	*%*
Poor technical recordings		152	52
Agreement between computer and physician		71	47
Good technical recordings		141	48
Agreement between computer and physician		81	58
Reasons for disagreement		60	42
Physician error	13%		
Physician criteria opinion differences	13%		
Imprecise criteria	10%		
Imprecise measurements	3%		
Lack of criteria	2%		
Noise and hardware problems	1%		
	42%		

*This analysis is one of several similar studies carried out over an 8 year period. The trends in the various areas have been similar and the study is judged representative of problems presented by physician-computer comparison studies.

Technician reaction

At the test hospital the ECG automated system was viewed by the technicians recording the electrocardiograms as one that added work As a test" and somewhat parallel system to the existing system In fact, it could be construed as adding work. Fifty two per cent of the total recordings made by the technicians for computer analysis had poor quality leads (noise and drastic baseline shifts) Even coding of sex had a 3 per cent error throughout the study Yet poor quality tracings were not in evidence in the heart station for the nonautomated existing system The technicians apparently edited or took greater care with them before submission to the electrocardiographer

The computer systems in use today still cannot cope as well with noise as humans. They will not produce a complete diagnosis when they cannot measure values in leads with poor technical quality In the group of tracings with missing or poor quality leads due to poor technician performance the physician agreed completely only 47 per cent of the time with the computer Complete physician-computer agreement in the group of tracings with good quality was 58 per cent Thus, poorly recorded leads may be one cause of physician-computer disagreement

Physician-computer comparison

No further analysis will be made of the 47 per cent poor quality recordings. In the remaining 58 per cent discussed below minor phraseology differences due to human variability or preference have been discounted. But why was the agreement only 58 per cent?

In 13 per cent of the good quality tracings, disagreement was due to physician error. In these the computer was, on review, correct. The computer pointed to findings which were present but which were missed by the cardiologist. These errors appear to result primarily from overly quick scanning by the physician. As examples a rate of 76 was called sinus tachycardia by the physician (probably looking at another tracing) whereas the computer had correctly labeled the rate. In several the computer correctly measured prolonged Q-T's or P-R's. The physician apparently missed the leads in which they were prolonged. Minor T wave abnormalities (low voltage) and other similar abnormalities were overlooked.

There was another 13 per cent disagreement due to differences in criteria used in the computer program and those used by the physician readers tested. In these cases the computer performed as programmed according to criteria fed into it. The computer criteria were evolved by "impartial physicians directing the computer program project by reviewing texts, calling in consultants, and testing criteria on three American and one foreign group of electrocardiographers. The differences in this 13 per cent "physician-computer" difference merely highlights the difference between criteria of different physician groups. It is not a computer system error. This finding should lead us to redefine our "standard" (our criteria). The finding of disagreement in this area has no logical basis to influence our acceptability of a computer output.

At the time of the study there was a 10 per cent physician-computer difference due to criteria which was not precise enough for the computer to accomplish what the physician designers wanted accomplished. This represents errors in physician-designer logic despite the use of texts, consultants, and field tests. These errors do not cause abnormality to be missed, but give poor or weak diagnostic categorizations. This group also includes arrhythmias (although atrial fibrillation and premature contractions are generally well categorized).

In 3 per cent of the tracings there were T-wave diagnostic errors accountable to computer measurement of wave forms. A few other wave forms were mismeasured but the "fail safe" steps in the existing program took care of all these mismeasurements, so they did not result in wrong diagnostic statements in this series. In our other series of similar studies, other wave measurements have caused diagnostic errors, but 3 per cent holds as a representative figure for a specific series.

In 2 per cent, criteria that should be incorporated at a later date but is not now in the program accounted for error. Presence of a pacemaker artifact or the lack of comparison with old electrocardiograms is included in this group.

In 1 per cent of the tracings, spurious noise in a specific lead that should have been detected by the computer but was not accounted for diagnostic disagreement. Hardware problems often cause these.

Fig. 1 is a flow diagram that outlines steps required to alter a computer program's logic and determine where improvements are needed when the errors are found. The chart indicates that both machine and man must be evaluated in evaluation of computer ECG output. Following the pathway shown can lead to develop-

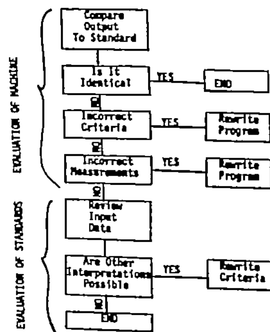


Fig. 1 Evaluation of computer-ECG output.

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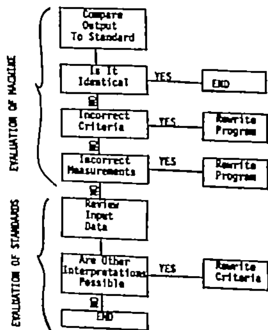


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line with variability figures reported in the literature.

Without these background considerations, computer analyses of ECG's could become an area of controversy and the great power, precision, and accuracy of the computer might fail to be used to medicine's advantage at the earliest date possible.

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ment of new computer (but not necessarily physician) criteria. This should result in computer physician agreement.

Comments

At the time of the study discussed in this communication computer system performance was 84 per cent that is 16 per cent of the statements produced were incorrect computer output. But the over all physician agreement with the system *appears* to be less. Physician-computer agreement will always appear to be less if the standard is not what it should be. In the study 26 per cent of the errors were due to the standard

Knowing the data for man and machine separately the theoretical limits of performance of the combined man machine system can be easily estimated If the machine operates with 84 per cent accuracy and physicians reproducibility is 74 per cent the maximum machine physician agreement possible is about 62% a value close to the observed value of 58 per cent noted in this study In other words the finding of only 58 per cent agreement between computer and physician represents almost the best figure attainable through a combination of both system accuracy and standard error or variability Both must be improved—not just one to have the best system

To increase physician agreement with the computer will require (1) the physician to write a more rigid universally acceptable standardized ECG criteria, as well as (2) a degree of increased machine performance. The latter is relatively easy although costly The former is not easy and far more costly

An advantage to the computer system is that the errors can be defined precisely so steps can be organized to correct them This has been the mode by which steady progress has been made in the computer electrocardiogram reading effort. It is expected that by the time of publication of this report the 10 per cent difference due to imprecise criteria will have been eliminated The locus of human variability cannot be predicted so corrective action cannot be taken.

The machine has in effect turned the tables on the physician and thrown the burden back to him He must now decide exactly what criteria should be to what degree they should be validated and at what probability level they should be included in a diagnostic or screening electrocardiogram

This is not to say that the physician cannot continue to perform with the subjectivity he has had in the past. But he should be aware of it when he dismisses or accepts a computer s assistance

Recommendations

First the technician must be considered and only one system imposed in any heart station Second from our experience we have learned it is best to have the computer ECG system in series (not in parallel) with the physician As such it is an aid to the physician it serves as a prescreening effort to help him increase his performance.

To make use of the computer as an aid the physician should first consider the computer s answer as the correct one. This will help avoid physician error such as the 13 per cent noted in this study There is one admonition that the physician not discount what the computer programmer tells him the computer cannot do This involves knowing a few items of data that can be learned in a few minutes.

He must then follow the set of criteria he has decided the computer is to follow This avoids most individual physician variability Official heart station criteria and terminology are mandatory to avoid physician physician differences brought out by this study as physician-computer disagreement

It is strongly suggested that interested groups begin to select and review nomenclature and diagnostic criteria This will allow development of formal methods for evaluating and updating standards for criteria.

In the final analysis, in order to make a judgment whether a computer system is ready for use the 16 per cent computer physician disagreement should be charged to faults in the computer system For proper comparison this 16 per cent should be contrasted with the 26 per cent error and variability of human readers as shown in this study That 26 per cent is not out of

timed vital capacity (FEV_1) functional residual capacity (FRC) *single breath carbon monoxide* diffusing capacity (DLCO) and carbon dioxide (pCO_2) in the expired air at the end of tidal volume and at the end of forced expiration. Derived calculations included residual volume (RV) total lung capacity (TLC) RV/TLC ratio and ΔpCO_2 (*pCO_2 forced expiration–pCO end tidal*) Conventional methods were employed.[14-23]

A standard 12 lead resting electrocardiogram (ECG) was recorded. The following ECG frontal plane parameters were obtained heart rate, PR interval (seconds) *maximum amplitude* (millivolts) and duration (seconds) of the P wave P wave contour (peaked, round, notched other) and mean P axes (Grant's method[24]) Amplitude and duration of the two components of the P wave in Lead V (*first or positive is designated P V and second or negative is P' V_1*) were also determined. ECG parameters were obtained by one observer (N B K.) and reviewed by another (J B C) in order to minimize observer variation.[25] P parameters were not obtainable in two patients, one with atrial fibrillation and one with wandering pacemaker

Chest roentgenograms, posterior-anterior and lateral taken during the same period, were interpreted by a radiologist (W W S.) *who had no access to other* clinical information. The radiographic parameters included cardiothoracic ratio estimate of heart size, and specific parenchymal and vascular evidence of obstructive lung disease.

Data were analyzed using an IBM 360/50 digital computer Conventional statistical methods were employed and the 5 per cent level of confidence was regarded as significant.[26]

Results

1 *ECG measurements.* The mean heart rate was 86 beats per minute with a range of *50 to 135 Seventy five per cent of the* patients had a normal rate, 3 per cent had sinus bradycardia and 22 per cent had sinus tachycardia. Normal sinus rhythm was present except for one case of atrial fibrillation and one case of wandering atrial pacemaker

The mean P R interval in the frontal plane was 0.157 ± 0.023 second with a range of 0.10 to 0 21 second Only one case had a P R interval in excess of 0 20 second

The mean values for the P wave parameters in the frontal plane and in Lead V with standard deviation and range are presented *in Table I and their distribution in* Tables II and III Only 5.8 per cent of the P waves were in excess of 0.11 second P wave amplitude was 0 25 mv or greater in 46.3 per cent of the patients.

P wave axis fell in the range of 0 to +60 degrees in 42 7 per cent 1 1 per cent were *to the left of this (−1 to −90 degrees) and* the remaining 56 1 per cent were to the right of +60 degrees (+61 to +269 degrees)

Analysis of P wave contour (Table IV) showed that in 35 cases (20 4 per cent) the P wave was rounded, in 94 cases (54 9 per cent) peaked in 5 (2 9 per cent) notched and in the remaining 37 cases (21 6 per cent) other contour Of the group with peaked P waves, two thirds had an amplitude below 0.25 mv Peaked high amplitude and notched P waves were associated with more rapid heart rate

Table I P wave parameters (n = 171)

Parameter	Duration (sec.)			Amplitude (mv.)			Axis (degrees)		
	Mean	S.D	Range	Mean	S.D	Range	Mean	S.D	Range
P Frontal plane	0.099	±0.014	0 04-0.13	0.22	±0.073	0 05-0 50	+70.98	±33.57	0-340
P V (+ component)	0.035	±0.015	0.00-0.08	0 06	±0 036	0 00-0.21			
P' V (− component)	0.026	±0 017	0 00-0 07	0 05	±0 037	0.00-0.19			

Clinical communications

P-wave changes in chronic obstructive pulmonary disease

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That P wave abnormalities in the electrocardiogram (ECG) reflect altered depolarization of the atria was recognized by Einthoven[1] in 1906. Pardee[2] in 1917 and Berliner and Master[3] in 1938 reported that tall peaked P waves in Leads II and III were found frequently in right atrial enlargement. Kahn[4] in 1927 was the first to note such P waves in patients with chronic lung disease (bronchial asthma) and several other early studies confirmed it.[5-7]

The advent of lung function tests has permitted more precise quantitation of impairment in chronic obstructive pulmonary disease (COPD) Thus, Wasserburger and associates[8] found that exaggeration of P waves in Leads II III and aV_F was qualitatively related to alterations in pulmonary function Spodick and associates[9] found that verticalization of the P axis as well as increased P wave amplitude was associated with more impaired lung function

Computer methodology permitted us to correlate P wave parameters with lung function and the chest roentgenograms, in order to determine which P wave changes are most valuable in the evaluation of patients with COPD

Methods

A group of 173 patients with COPD who were referred for pulmonary function tests was studied Of these 68 2 per cent were male and 31 8 per cent female with a mean age of 60 1 and 53 5 years, respectively

The pulmonary function measurements included vital capacity (VC) maximum voluntary ventilation (MVV) 1 second

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Table IV. P wave contour in limb leads versus rate (n = 171)

Contour		No. of cases	Mean heart rate	Range		%	
				Low	High		
Round		35	83.5	54	110	20	
Peaked	Less than 0.25 mv	63	84.5	58	120	37	55
	0.25 mv or more	31	99.2	68	136	18	
Notched		5	98.8	71	136	3	
Other		37	78.1	46	115	22	
Total		171				100	

with the least impaired patients designated as quartile I and the most impaired designated IV. The mean value for all the ECG parameters were calculated for each quartile. A typical set of such results, MVV data, is related to frontal plane measurements in Tables V and VI.

In patients with the most severe pulmonary impairment (quartile IV) heart rate was greater. P amplitude was augmented and the frontal plane P axis was rightwardly shifted to a statistically significant degree (F test). P-R interval and P duration were not significantly changed as lung function worsened. In Lead V_1, P amplitude was highest in quartile I and P′ amplitude was lowest. F test showed no over-all difference among quartiles, but the t test of the difference between quartiles I and IV was significant. P V_1 and P′ V_1 durations showed no difference related to lung function.

Identical quartile analyses were performed with VC, FEV, RV/TLC, DLCO, forced expiratory pCO_2, and ΔpCO_2, and they showed similar trends with FEV, RV/TLC ratio, and VC comparable to MVV values. The others gave inferior separation of ECG parameters.

3. *Relation of P wave parameters to QRS axis.* In considering the significance of the above quartile data it was realized that the two patients with left axis deviation (LAD) of the P wave in the frontal plane (coded for computer analysis as +330 and +340 degrees) could distort the results. In addition, patients with LAD of the mean QRS often have coronary artery disease[14] and thus might influence the P wave. Therefore, an analysis was performed in which the patients with left axis deviation of the mean P and of the mean QRS axes in the frontal plane were removed, but no changes in the trends resulted.

In order to determine more specifically whether LAD of the mean QRS altered the P wave, the cases were divided into 150 (89 per cent) without LAD and 19 (11 per cent) with it (Table VII). There was no difference between the two groups in heart rate, P-R interval, P duration, P amplitude, QRS duration, and QRS amplitude. The mean P axis was slightly shifted to the right in the group with LAD of the QRS but not significantly. Thus, patients with LAD of the QRS exhibited the same rightward shift of the P axis as those without LAD.

4. *Correlation of lung function with P-wave parameters* (Table VIII). Frontal plane P amplitude and axis were consistently negatively correlated with lung function to a significant degree, and P axis correlation coefficients were higher than P amplitude. Heart rate was similarly correlated with VC, MVV, and RV/TLC ratio. P amplitude and duration in V showed a positive relationship to several lung functions, but were not consistent, and P′ parameters had no significant relationship.

5. *Criteria for abnormality.* The percentage of patients with abnormal P values was determined for each MVV quartile (Table V). Using +75 degrees as the criteria for P wave axis, 70.4 per cent of the patients

Table II. Distribution of P wave parameters in the frontal plane (n = 171)

Duration (sec.)			Amplitude (mv.)			Axis (degrees)			Per cent
Seconds	No.	Per cent	Millivolts	No.	Per cent	Degrees	No.	Per cent	
0.04–0.05	2	1	0.05–0.09	2	1	−30	1	1	1 (n = 2)
0.06–0.07	12	7	0.10–0.14	15	9	−20	1	1	
0.08–0.09	88	51	0.15–0.19	26	15	0	2	1	43 (n = 73)
0.10–0.11	59	35	0.20–0.24	49	29	10	2	1	
0.12–0.13	10	6	0.25–0.29	38	22	20	2	1	
			0.30–0.34	31	18	30	2	1	
			0.35–0.39	5	3	40	2	1	
			0.40–0.44	2	1	50	20	12	
			0.45–0.49	1	1	60	43	25	
			0.50–0.54	2	1	70	20	12	56 (n = 96)
						80	56	32	
						90	19	11	
						100–109	1	1	
Total	171	100		171	100		171	100	100

Table III. Distribution of P wave parameters in Lead V_1 (n = 170)*

	Duration				Amplitude				
	P (+)		P′ (−)		Millivolts	P (+)		P′ (−)	
Seconds	No.	Per cent	No.	Per cent		No.	Per cent	No.	Per cent
0.00	9	5	32	19	0.00	9	5	32	19
0.01	1	1	5	3	0.01–0.04	37	22	44	26
0.02	23	13	39	23	0.05–0.09	79	46	64	37
0.03	50	29	41	24	0.10–0.14	41	24	29	17
0.04	54	32	37	22	0.15–0.19	3	2	1	1
0.05	10	6	6	3	0.20–0.24	1	1		
0.06	22	13	10	6	0.25–0.39				
0.07	1	1	0	0					
0.08									
Total	170*	100	170	100		170	100	170	100

*In one case, Lead V_1 was technically unsatisfactory.

The mean values for the P V_1 (duration and amplitude) were slightly greater than those of P′ V_1. In 9 cases (5.3 per cent) P V_1 was absent (Table III). In about 20 per cent P V_1 duration was 0.05 second or greater. In 32 cases (18.8 per cent) P′ V_1 was absent. In only 10 per cent of the cases P′ V_1 duration was 0.05 second or greater

In 45 cases (26.4 per cent) P V_1 amplitude was 0.10 mv. or more. In 30 cases (17.7 per cent) P′ V_1 amplitude was 0.10 mv. or more.

2. *Relation between pulmonary function and P wave parameters* (Tables V and VI). The patients were divided into four quartiles on the basis of each lung function test

P axis (degrees)		P-R interval (sec.)		P amplitude* 0.25 mv. or more		P axis 75° or more	
Mean	S.D	Mean	S.D				
59 8	±22	0 155	±0 02	37 2%	(33 3)	27 9%	(22 2)
76 9	±43	0 157	±0 02	41 8%	(45 9)	48 8%	(45 9)
78 2	±44	0 163	±0 02	48 8%	(47 4)	39 5%	(34 2)
78 2	±13	0 154	±0 02	54 5%	(56 1)	70 4%	(70 7)

...s are presented within the parentheses.

Table VII. Effect of LAD of the mean QRS upon P-wave parameters

Parameter	Total		No LAD		LAD	
	(n = 169)		(n = 150)		(n = 19)	
	Mean	S.D	Mean	S.D	Mean	S.D
Heart rate (min.)	86 36	±17 65	86 48	±17 82	85 37	±16 70
P-R interval (sec.)	0 157	± 0 023	0 157	± 0 023	0 159	± 0 021
P duration (sec.)	0 090	± 0 014	0 090	± 0 014	0 089	± 0 016
P amplitude (mv.)	0 22	± 0 075	0 23	± 0 070	0 22	± 0 070
P axis (degrees)	+70 12	±18 06	+69 88	±17 36	+72 00	±23 31
QRS axis (degrees)	+100 44	±89 95	+71 54	±43 07	+319 47 (−40 53)	±27 48

*LAD defined as mean QRS axis in the frontal plane of −1 to −90° (+180° to +270°). For the computer calculations, 2 cases with LAD of the mean P (−30° and −30°) were considered as +330° and +340° respectively and are not included in this table.

frontal plane is less than 0 25 mv.[4,1] Of our series, 46.2 per cent exceeded this value. In Spodick's[9] series of patients with COPD 13 9 per cent were in excess of 0 25 mv while in Chappell's[20] series, 25 percent of patients with severe emphysema and 5 7 per cent of those with mild emphysema exhibited this change. Caird and Wilcken[21] found the incidence of "P pulmonale" to be 15.5 per cent. In view of the demonstrated relationship between P amplitude and lung function tests, the different percentage of patients with increased P amplitude in each series will depend in part upon the level of lung function. In addition, there is the intrinsic myocardial factor discussed by Berliner and Master who stated that "a failing heart is known often to show low voltage of the ventricular complex. By the same token, the voltage of the auricular wave must be influenced by variations in the functional status of the auricular musculature. It is no wonder therefore, that marked auricular hypertrophy is occasionally found to be associated with P wave of normal height."

Our group found that mean P wave axis in the frontal plane for 500 normal adults with mean age of 44 years was +60 degrees.[22] Other authors[17,23,24] have reported the normal P axis to be somewhat less than this (+46.5 +49 and +45 degrees, respectively) In this study 56 per cent of the patients had a mean P-axis value of +70

Table V P wave parameters versus maximum voluntary ventilation (MVV) (n = 173)*

Quartile	n	MVV L/M Mean	MVV L/M S.D	Heart rate (min) Mean	Heart rate (min) S.D	P duration (sec.) Mean	P duration (sec.) S.D	P amplitude (mv) Mean	P amplitude (mv) SD
I	43	108 8	±25 1	82 1	±15 6	0 09	±0 02	0 21	±0 07
II	43	63 8	±8 2	81 3	±17 2	0 09	±0 01	0 22	±0 07
III	43	44 8	±4 9	84 5	±16 9	0 09	±0 01	0 25	±0 09
IV	44	27 8	±5 6	92 1	±19 4	0 09	±0 01	0 25	±0 09
Total	173								

*The 19 cases with LAD of the mean QRS and 2 cases with LAD of the mean P were excluded and the values found for the remaining

Table VI P wave parameters in Lead V_1 versus maximum voluntary ventilation (n = 170)*

Quartile	n	MVV L/M Mean	MVV L/M S D	P V (+) Duration (sec) Mean	P V (+) Duration (sec) S.D	P V (+) Amplitude (mv) Mean	P V (+) Amplitude (mv) S.D	P′ V_1 (−) Duration (sec) Mean	P′ V_1 (−) Duration (sec) S.D	P′ V_1 (−) Amplitude (mv) Mean	P′ V_1 (−) Amplitude (mv) S.D
I	42	108.8	±25 1	0 036	±0.016	0.075	±0.042	0.022	±0.016	0 047	±0 038
II	43	63.8	±8.2	0 035	±0.013	0 063	±0 030	0.028	±0.016	0.053	±0.034
III	42	44.8	±4 9	0 036	±0 013	0.066	±0 030	0.023	±0.015	0.043	±0.033
IV	43	27 8	±5 6	0 032	±0.015	0 058	±0 040	0.030	±0.017	0.056	±0.040
Total	170										

*In one case, Lead V_1 was technically unsatisfactory

in quartile IV were abnormal versus 27 9 per cent in quartile I Using 0 25 mv or more as the criteria for P wave amplitude 54.5 per cent of quartile IV were abnormal versus 37 2 per cent of quartile I There fore, P wave axis criteria were better both in sensitivity and specificity Similar calculations performed excluding 19 cases with LAD of the QRS and 2 cases of LAD of P gave the same findings.

6 *ECG radiographic correlation* (Table IX) Frontal plane P amplitude and axis showed a negative correlation with cardiothoracic ratio but there was no relation between ECG parameters and x ray evidence of right or left ventricular enlargement. Consistently positive correlations of P amplitude and axis were present with roentgenographic signs of COPD but heart rate P wave duration P R interval and P wave parameters in V_1 had no significant correlation with them

Discussion

As a group these patients had distinct deviations from normal P parameters. Duration of the P wave in patients with COPD might be expected to be normal since only the initial or right atrial portion is altered and its prolongation is hidden in the second or left atrial portion of the P wave Our observed values fulfilled this expectation [17, 6] This is in contrast to the situation in mitral stenosis in which 69 per cent of the cases had a prolonged P wave [18]

The normal P wave amplitude in the

Table IX. Correlation of ECG with radiographic parameters (n = 147)

Parameters	Frontal plane					Lead V			
	Heart rate	P dur	P amp.	P axis	P R int.	P dur	P′ dur	P amp.	P′ amp
Peripheral pulmonary artery caliber	+0.03	0.00	+0.20*	+0.28†	+0.04	−0.04	−0.09	−0.06	−0.12
Main pulmonary artery enlargement	−0.04	−0.04	+0.02	+0.03	+0.02	−0.10	0.00	−0.02	+0.12
Vascular branching	+0.14	+0.06	+0.06	+0.28†	+0.04	+0.02	+0.05	−0.02	−0.01
Diameter pulmonary artery RLL	+0.13	+0.06	−0.01	+0.13	+0.06	+0.10	+0.14	+0.07	+0.07
Cardiac size	−0.04	+0.03	−0.06	−0.09	+0.11	+0.07	+0.02	+0.13	+0.13
Cardiothoracic ratio	−0.01	−0.01	−0.20*	−0.22*	+0.04	+0.06	−0.03	+0.07	+0.03
Right ventricular enlargement	−0.01	+0.05	+0.02	0.00	+0.03	+0.02	+0.05	+0.06	+0.17
Left ventricular enlargement	−0.03	+0.02	−0.03	−0.09	+0.13	+0.11	+0.02	+0.13	+0.08
Bullae and blebs	+0.10	−0.03	+0.11	+0.28†	−0.01	−0.14	−0.04	−0.17	−0.11
Hyperradiolucency	+0.03	+0.02	+0.23†	+0.29†	+0.02	−0.03	−0.06	−0.07	−0.13
Right diaphragm dome, interspace	+0.08	+0.02	+0.25†	+0.37†	−0.04	−0.09	+0.03	−0.09	+0.01
Left diaphragm dome, interspace	+0.09	+0.03	+0.32†	+0.36†	−0.09	−0.08	+0.06	−0.08	0.00
Diaphragm position	+0.05	0.00	+0.24†	+0.44†	0.00	−0.09	−0.08	−0.09	−0.15
Diaphragm contour	+0.08	−0.01	+0.23†	+0.39†	−0.03	−0.09	−0.10	−0.10	−0.18
Retrosternal space	+0.14	+0.07	−0.02	+0.17	+0.12	−0.02	+0.01	−0.03	−0.07
Diffuse fibrosis	+0.03	−0.03	−0.09	+0.18	−0.03	−0.10	−0.02	−0.10	−0.01
Focal fibrosis	+0.17	+0.04	−0.02	+0.22†	−0.01	−0.06	+0.11	−0.05	+0.10

Abbreviations: Dur., duration; amp., amplitude; Int., interval.
*P <0.05 when r 0.16 to 0.22.
†P <0.01 r 0.22 or more.

the ECG.[11] Another element might be the presence of forms of heart disease other than those resulting from lung disease. In addition to the fact that about 10 per cent of patients with emphysema have LAD of the QRS,[14] Caird and Wilcken[11] showed that left ventricular hypertrophy was present at autopsy in half of their COPD patients. For these reasons our demonstration of the utility of the P wave changes in patients with COPD and LAD of the QRS has particular significance, indicating reliability in the presence of presumed left ventricular disease. The low incidence of arrhythmias previously reported in patients with COPD[20] is confirmed in this series.

The alterations of the ECG reported here are quantitatively related to the observed abnormalities of lung function. When lung function is minimally impaired (quartile I) there was no significant difference from normal in frontal plane P parameters, but as lung function deteriorated (quartile IV) the increase in P amplitude and rightward shift of axis was striking. Our findings are similar to Spodick and to Chappell who found relationships of the P axis to lung function impairment utilizing FEV_1[9] and peak expiratory flow rate (PEF) and FEV_1,[10] respectively but contrary to the findings of Caird and Wilcken[11] who reported that while P amplitude was more frequently elevated when FEV was below 45 per cent, there was no relationship between the P axis and FEV_1. The P wave contour did not appear to offer any information not present in P amplitude. This is in keeping with Spodick's findings that Gothic P wave" (peaked but lower than 0.25 *mv*) was not related to lung function changes. There was, however a reversal of

Table VIII *Correlation of ECG parameters with lung function tests* ($n = 168$)

Parameters	*Frontal plane*					*Lead* V_1			
	Heart rate	*P dur*	*P amp*	*P axis*	*P R int.*	*P dur*	*P' dur*	*P amp*	*P' amp.*
Total lung capacity (c.c.)	0 02	−0.04	0 09	0.24	0.14	−0.16	−0.03	−0.10	−0.02
Residual volume (c.c.)	0.19	−0.02	0.25†	0 44†	0 08	−0.26†	0.07	−0.23†	0.02
RV/TLC (%)	0.30†	0.02	0 27†	0.44†	0.03	−0.23†	0.13	−0.24†	0.06
pCO	0 12	0.00	0.15	0.29†	0.10	−0 02	−0.01	−0.09	−0.01
Diffusing capacity	0.00	−0.23	−0.07	−0.23†	−0 06	0.07	−0.17	0.06	−0.16
Vital capacity (c.c.)	−0.22†	−0.05	−0.15	−0.23†	0.05	0.07	−0.11	0.14	−0.04
One second volume (c.c.)	−0 19*	−0.11	−0 22†	−0.45†	−0.02	0.19	−0.07	0.26†	0.01
Maximum voluntary ventilation (L./min.)	−0.20†	−0.04	−0 19	−0.35†	−0.06	0.12	−0.10	0.22†	0.00

Three cases are not included, 2 with LAD of the P wave and one with Lead V technically unsatisfactory
Abbreviations Dur. = *duration*, amp. = amplitude; int. = interval.
*$0.01 < p < 0.05$ when = 0.15 to 0.19
†$p < 0.01$ when = 0.20 or more.

degrees or more. This rightward shift of the P axis in COPD has been found by other authors Zuckermann and associates[23] found a P axis of +60 degrees or more in 82 per cent, Spodick and co-workers[9] and Caird and Wilcken[21] found a P axis of +70 degrees or more in 73 and 79 per cent respectively and Chappell[18] found an axis of +75 degrees or more in 29 per cent. In our study only one case exceeded +90 degrees indicating that in patients with COPD right axis deviation of the mean P axis is rarely found This is in agreement with Lipman and Massie.[24] Only 1 per cent had a mean P axis in the left axis deviation quadrant and the possibility of ectopic atrial pacemaker should be considered

Grant[14] reported that about 10 per cent of patients with pulmonary emphysema have LAD of the mean QRS comparable to our prevalence of 12 1 per cent. Such leftward shift of the QRS is frequently described in patients with coronary heart disease[14,27] and in such patients the P axis remains normally directed[28] despite the leftward QRS shift. Thus, our finding that the P axis is independent of the QRS axis is not unique to COPD

The normal P wave in Lead V_1 is usually diphasic of the + − type. The first or positive component is due predominantly to right atrial depolarization and the second or negative component to the left Morris[21] series of 100 normal subjects showed a P V_1 duration of 0 05 second amplitude of 0 06 mv and a P' V_1 duration of 0 02 second and amplitude of 0 05 mv To make Dines and Parkins[24] data on 50 normal subjects comparable to Morris and to this series a recalculation was necessary giving values for P V_1 of 0 04 second and 0 08 mv and for P' V_1 0 02 second and 0 05 mv The data on our patients with COPD are similar to the data on these normal subjects (Table I)

Our correlation data and quartile analysis suggest that P V_1 parameters decreased as lung function worsened which may represent increased insulation effect. However the error of measurement of such small components is high and better methods for amplification and recording are required if their significance is to be fully determined

Impressive as some of the P relationships are with lung function the correlation coefficients are moderate in value and the findings do not indicate that lung function is the sole determinant of ECG parameters in COPD Other features in the natural history of the lung disease may make important contributions to the ECG findings. For example the patient with chronic bronchitis is more likely to develop cardiac decompensation than the patients with pure emphysema and variables such as this might be important in the evolution of

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the relation between P contour and heart rate which Gross[33] defined for normal subjects. He found a higher incidence of peaked P wave with lower heart rate while in COPD the opposite occurred

We have not used the term cor pulmonale in this discussion because proof of this is ultimately anatomical based upon the thickness of the right ventricular wall and because the clinical diagnosis of pure cor pulmonale in the absence of any other heart abnormality is often inconclusive [34,35] The observed ECG alterations might be attributed to either primarily pulmonary or cardiovascular factors or both The pulmonary factors include hyperinflation of the lungs which might increase insulation depress the diaphragm and cause the heart to assume a more vertical position and to rotate clockwise on its points of fixation at the great vessels. The possible vascular factors include anatomical narrowing of the pulmonary vascular bed and/or vasoconstriction due to hypoxemia pulmonary hypertension and overload of the right ventricle and ultimately the right atrium The insulation effect does not appear to be significant with respect to the frontal plane because P amplitude increased as pulmonary disease became more marked The rotational effect may well be important because the observed P-axis shift did not reflect any visible radiologic abnormality of the heart but did correlate well with pulmonary abnormality Pulmonary hypertension hypoxemia, and right sided overload may be significant in COPD patients but Fowler and associates[34] showed that patients with cor pulmonale due to causes other than emphysema did not exhibit the same degree of rightward P-axis shift. Caird and Wilcken state that none of the P wave findings was significantly related to the state of the right atrium as recorded at post mortem but their finding of P pulmonale in 7 of 17 autopsied patients with an abnormal right atrium and in 2 of 9 patients with normal right atrium does suggest such a relationship albeit imperfect Thus there is relatively good precision with respect to description of the P wave changes which occur in COPD but uncertainty with respect to the exact mechanisms involved in their production Nevertheless the P wave observations reported here comprise a useful basis for detecting the effects of COPD upon the P wave regardless of mechanism.

Summary and conclusions

The relationship of the P wave changes to lung function tests and to quantitatively described chest x rays was determined in 173 patients with chronic obstructive pulmonary disease (COPD) P axis (frontal plane) was to the right of +70 degrees in 56 per cent of the cases. In 46 per cent P amplitude was 0 25 mv or more. P duration was normal P amplitude and duration values in Lead V_1 showed no significant deviation from normal. The population was divided into quartiles on the basis of maximum voluntary ventilation quartile I being the least impaired P amplitude in excess of 0 25 mv was present in 37 per cent of the cases in quartile I and 55 per cent in quartile IV P axis in excess of +75 degrees was found in 28 per cent of patients in quartile I and 70 per cent in quartile IV These P wave changes persisted in the presence of left axis deviation of the QRS Correlation with lung function was consistently greater for P axis than for P amplitude. Correlation of P wave values was poor with x ray parameters indicative of heart disease but was good with those indicative of lung disease This study confirms and quantitates the importance of P wave amplitude and axis in COPD and proves that rightward shift of P axis is the most discriminating P wave change in evaluating the severity of COPD

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only according to age and geographic location. Blood pressure levels were determined in both members of the pair in every case. The opportunity to carry out such a study was provided through the use of the Connecticut Twin Registry which contains a record of all multiple births occurring in Connecticut since 1897 and also a file indicating the current address of many of the twins.

Methods

The first step was to send a letter to like-sexed pairs of twins in the vicinity of Hartford over the age of 40 requesting permission for one of us (R V) to visit them in

Table I Observations in all twin pairs with hypertension

No.	Age and sex	Blood pressure on visit		Marital status no. children	Weight now and change since age 20
		No. 1	No. 2		
		Monozygotic†			
1H	51, F	164/118	168/108	M, 2	118 (−16)
2H		160/114 (Rx)	156/106 (Rx)	M 2	118 (−17)
3H	63, F	186/112	190/ 96	S, 0	165 (+46)
4		222/116	182/ 90	S, 0	185 (+66)
5H	51, M	190/116 (Rx)	188/102 (Rx)	M 3	135 (+15)
6H		192/102	200/110	M 2	190 (+25)
7H	43 M	164/100	178/ 98	M 2	168 (+38)
8H		156/100	146/ 96	M, 0	179 (+29)
9H	43 F	138/ 95	—	M 1	180 (+50)
10H		152/104	—	M, 2	175 (+45)
		Dizygotic-concordant†			
11H	46, M	240/144	162/104	M 2	190 (+55)
12H		194/108	174/102	M, 2	174 (+39)
13H	66, F	194/106	184/100	W 0	180 (+50)
14H		164/ 94 (Rx)	166/100 (Rx)	M 6	155 (+55)
15H	61 M	134/100	154/102	S, 0	160 (+30)
16H		168/ 88 (Rx)	158/ 86 (Rx)	S, 0	179 (+ 4)
		Dizygotic-discordant†			
17H	40, F	144/ 82 (Rx)	164/100 (Rx)	M, 0	140 (−10)
18		132/ 96	134/ 80	W 1	190 (+40)
19H	56, F	188/110 (Rx)	174/ 98 (Rx)‡	M, 1	120 (+20)
20		136/ 86	124/ 72‡	M, 0	128 (+23)
21H	56, F	200/104	190/104‡	S, 0	95 (−20)
22		130/ 90	106/ 78‡	M, 1	127 (+12)
23H	47 F	162/100	156/104	M 3	198 (+79)
24		114/ 80	—	M 0	97 (− 3)
25H	59 F	160/104	132/ 96‡	M 1	145 (+25)
26		134/ 80	118/ 76‡	M, 2	130 (+ 5)
27H	50, F	154/ 98	126/ 80 (Rx)	M 1	145 (+25)
28		110/ 72	—	D 2	
29H	41, F	158/ 98	144/ 96	M 3	122 (+26)
30		114/ 70	102/ 68	M 2	126 (+ 8)
31H	52, M	184/ 96	—	M, 2	185 (+55)
32		150/ 86	—	M 1	150 (+25)
33H	56, F	164/ 96 (Rx)	130/ 74 (R)	S, 0	146 (+26)
34		150/ 80	142/ 80	S, 0	152 (+34)

*Defined as diastolic blood pressure above 94 mm. Hg on first visit. "H" (which appears after the subject no.) means, by arbitrary definition, that the individual was considered hypertensive (blood pressure in excess of 94 mm. Hg on second visit) or under treatment for hypertension.
†Zygosity based on appearance, concordance in blood groups, and opinion of twins themselves.
‡Second blood pressure taken from records at State Health Department examination.
M, Married; S, single; D, divorced; W widowed (Rx), under antihypertensive treatment.

A study of hypertension in twins

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Patients with arterial hypertension are frequently found to have a strongly positive family history for this condition. To shed more light on the possible role of genetic influences in this disease, a systematic study of identical and fraternal twins was undertaken. For many years research interest has been drawn to the possibility that a genetic basis may exist for the common hypertension that appears in middle age without apparent cause. Considerable evidence has accumulated suggesting that there is an inheritance factor which probably represents multiple genetic influences. Familial studies therefore continue to provide practical information of various kinds, and in particular the study of twins helps to shed light on pathogenesis and the question of environmental versus genetic factors.

A number of authors[1-7] have reported concordant hypertension in identical twins. Only Friedman and Kasanin[8] have reported discordant hypertension in a single pair of twins with identical blood groups but widely divergent personalities. However, most of these studies of concordance have been influenced adversely by the ascertainment factor—that is, that when a physician learns that his hypertensive patient has an identical twin and finds that the twin's blood pressure also is elevated, he is more likely to report his findings than if the sibling were found normotensive. Consequently, the true concordance rates for hypertension in identical twins is not known.

Another problem in twin studies is that essential hypertension is a disease which expresses itself late in life[1,9]; hence if the twins studied were young and the disease became apparent earlier in one twin than the other, poor concordance between blood pressure levels might be observed at any given time.

In the study reported here, the ascertainment factor was almost negligible because the sample was comprised of twins selected

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is too small to establish a statistically significant difference.

The prevalence of *elevated* blood pressure (12.2 per cent) in the identical twin sample resembles that in the general population of a similar age. Thus, unless the expression of this condition is different in twins than in the population at large it may be concluded that most cases of essential hypertension which appear in late middle-age are determined by heredity

Physicians records in the case of two monozygotic twin pairs support the view that among genetically predisposed individuals the condition may develop at different ages, perhaps dependent on environmental factors but that the overall result of inherited influences will nevertheless become manifest in the fifth or sixth decade of life with remarkable uniformity This view supports the important observations of Platt cited previously If a predisposition to hypertension could be identified early in life surveillance and appropriate early treatment would be of great practical importance.

Summary

A study of the blood pressure of 86 pairs of like-sexed twins over age 40 selected at random was performed Twelve per cent were found to have a diastolic blood pressure in excess of 94 mm. Hg In 4 out of 5 identical twin sets both members were found to have hypertension of about equal magnitude. In the fifth set, the predetermined definition of diastolic hypertension was not met in one member of the pair although the systolic blood pressure was clearly elevated. In two identical twin sets, where *information concerning previous* blood pressure could be obtained the age of onset of the hypertension differed. Among *the 49 dizygotic twin sets*, diastolic hypertension was found in 15 per cent of the individuals. In 3 of 12 of these pairs, it was present in both members.

Since the prevalence of hypertension after age 40 in the identical twin sample resembles that in the population at large, it is concluded that the ultimate development of this condition is heavily dependent on genetic influences.

The authors express their indebtedness to the late Dr A. C. Corcoran, who contributed much to *the planning of the project*

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their homes to obtain information for a questionnaire The purpose of the study was not mentioned in the letter Favorable replies came from 86 pairs of twins repre senting 85 per cent of the number of twin sets contacted by mail

At the home visit after completing a brief questionnaire the examiner deter mined the sitting blood pressure three times on the right arm then on the left then again three times on the right. The last three readings (using fifth phase as diastolic end point) were averaged and recorded as the blood pressure of the propositus To prevent bias, the examiner purposely avoided having knowledge of the blood pressure of the sibling of the twin he was examining If the diastolic blood pressure was above 94 mm Hg a second visit was requested for both the twin and his sibling The twin was considered to be hypertensive if the blood pressure remained above 94 or if he was known to be under treatment for hypertension In a few in stances where readings had been taken previously in the course of a health depart ment examination these were used as sec ond readings. On the second visit blood was obtained for confirmation of zygosity

Results

Among the 86 twin pairs examined hy pertension was found in 17 sets of twins, 5 of them monozygotic. As shown in Table I 24 individuals in the 17 twin sets showed hypertension according to the criteria for this study In 3 cases hypertension was noted at the first visit but a repeat visit could not be made

There were 37 pairs of monozygotic twins over age 40 in the study hypertension was found in 9 individuals or 12 2 per cent of this group In one instance (twin no 4) the diastolic blood pressure fell below 95 mm Hg on the second visit but the systolic pressure remained within the hypertensive range. This was the oldest pair of identical twins and the only one of 5 identical sets in which hypertension might be considered discordant. The magnitude of diastolic blood pressure elevation was comparable in each twin set being within a range of 10 mm Hg in all of the identical twins.

Although the sample size is limited a calculation by the chi square method with Yates correction for continuity shows an increased concordance of hypertension in monozygotic twins at about the 6 per cent level of confidence.

There were 49 pairs of dizygotic twins included in the study 15 individuals or 15 3 per cent of the sample were considered hypertensive. In 3 of 12 dizygotic twin sets each member was found to be hypertensive. In 9 other pairs only one member was hypertensive

A variety of additional observations are listed in Table I Certain variables commonly thought to be associated with hyper tension such as weight changes, sex marital status, and number of pregnancies, did not seem to affect concordance rates in the identical twins. They had lived apart for a median period of 16 years.

In two pairs of identical twins (nos. 1 and 2 5 and 6) the age at onset of hyper tension differed considerably as indicated by a study of the records and by corre spondence with the family physicians in volved In the first pair twin no. 2 ex hibited hypertension (140/100) at the age of 35 whereas her partner s blood pressure presumably remained normal until at least age 49 when she reported that she had been permitted to donate blood Yet two years later both twins showed hyper tension of about an equal magnitude. Similarly the blood pressure in twin no. 5 was reported by his physician to have been 124/80 at age 32 while his sibling had a blood pressure of 160/100 at about the same time at age 51 both showed a com parable blood pressure level

Discussion

The remarkably high degree of con cordance for hypertension between pairs of identical twins over age 40 selected at random from the general population leaves the impression that this condition is under a very strong genetic influence It is un fortunate that the material is too limited to yield a value of high statistical sig nificance (p = 0 06) Twenty five per cent of dizygotic twin pairs showed concordance rates for hypertension This again suggests that a genetic influence plays an important part in this disease since the frequency of this condition in the total population stud ied was only 15 per cent. Again the sample

Table 1

Failing implanted unit	*Temporary external unit on right ventricular catheter*		
	Fixed-rate	*Demand*	*Ventricular-triggered pacemaker*
Fixed-rate	*Not suitable*	*Set rate slightly faster (5 beats/min.) and slowly reduce*	Set rate slower to "lock on" to implanted unit
Demand	Set rate faster	Set rate faster to pace heart and inhibit implanted unit	Set rate faster to pace heart and inhibit implanted unit
Ventricular-triggered	Set rate faster	Set rate faster to pace heart. Implanted unit will "lock on" to external unit	Set rate faster (to pace heart) or slower (to "lock on" to implanted unit)

*Competition will be produced if the heart responds intermittently to the uninhibited pacemaker.

continuously but the resulting ventricular rate will not be that set on the controls of the demand pacemaker. Each impulse from the demand pacemaker causes ventricular contraction but the pacemaker is then recycled from the ineffective stimuli provided by the implanted unit. Impulses from the implanted pacemaker do not cause ventricular contraction because they always fall in the refractory period of the beat caused by the external demand pacemaker. The function of the impulses from the implanted unit is thus merely to reset the demand pacemaker after each heart beat so that the final ventricular rate is that of the implanted unit, not that of the demand pacemaker. If the standby rate of the demand unit is slowly reduced, the stimuli from the two pacemakers will become closer together so that careful adjustment of the standby rate of the demand pacemaker will result in stable continuous pacing without significant distortion of the QRS complex (Fig. 1, second and third ECG strips).

This method of arranging for a temporary external demand pacemaker to "lock on" to the implanted pacemaker rate depends upon there being a very short or nonexistent blocking time of the amplifier in the demand pacemaker. This is the case with most apparatus commercially available.

VENTRICULAR TRIGGERED PACING. An alternative method of approach is for an external ventricular triggered pacemaker to be used. If the standby rate of this pacemaker is set slower than that of the implanted failing unit, the external pacemaker will be triggered by the stimuli from the implanted pacemaker and will then immediately pace the heart. The heart rate will then be that of the implanted failing pacemaker but the actual contraction will in most instances be initiated by the impulses from the external triggered pacemaker (Fig. 2). If the ventricular triggered pacemaker standby rate is set faster than that of the implanted pacemaker, the resultant rhythm will be made up of short periods of paced tachycardia but there will be no period of ventricular asystole.

SPONTANEOUS ECTOPIC BEATS. If occasional ectopic beats occur when the external pacemaker is of the demand type, the rhythm becomes temporarily irregular with the possibility of a postectopic pause equivalent to the escape interval of the demand pacemaker. If the external pacemaker is of ventricular triggered type, there will be no such postectopic pause since the next impulse from the implanted pacemaker will trigger the external unit.

CLINICAL IMPLICATIONS. With either of these two methods of temporary control of

Emergency management of patients with "missed pacing"

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It is frequently difficult to manage patients with implanted pacemakers when the heart is not consistently responding to the pacing impulse. This can occur when the battery voltage is reduced when the electrode is detached from the heart when exit block (high threshold) is present when an electronic component has failed or when one or more of the electrodes is broken. In all these situations the implanted pacemaker may produce impulses but these do not always produce cardiac contraction so that bradycardia or syncopal attacks are likely Nevertheless, the impulse may inhibit a demand pacemaker which is being used in conjunction with a temporary transvenous electrode and if some of the stimuli from the implanted unit produce cardiac contraction then the use of a temporary external fixed rate pacemaker may result in competition

The purpose of this paper is to describe the technique of management for patients in this situation and all the methods described have been satisfactorily applied in patients. The management of patients with pacemaker tachycardia (run away pacemaker racemaker) is an emergency procedure involving immediate disconnection of the pacemaker from the heart and is not dealt with in this communication It is now fortunately very rare.

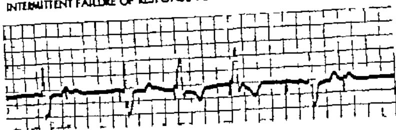
Techniques of management (Table I)

Management with implanted asynchronous (fixed rate) pacemaker A temporary transvenous electrode is passed into the right ventricle in the usual way and connected to an external pacemaker which may be one of two types demand or ventricular triggered

DEMAND PACEMAKERS If the demand pacemaker is set with a standby rate slower than the implanted pacemaker it will be continually inhibited and therefore ineffective. If it is set considerably faster than the implanted pacemaker there will be an irregular rhythm with the demand pacemaker sometimes driving the heart and sometimes being inhibited (Fig 1 lower ECG) This is likely to result in an irregular rhythm and there may be short bursts of paced tachycardia and relatively long periods of ventricular asystole

If the standby rate of the demand pacemaker is initially set faster than that of the implanted unit, but is then reduced until it is only slightly above that of the fixed rate pacemaker the stimuli from the demand pacemaker will drive the heart

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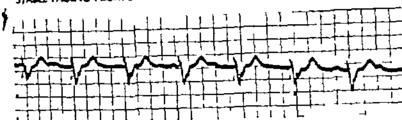




Fig. 2. *Upper trace.* The second impulse falls during the vulnerable period of the first (spontaneous) beat. The impulse is detected from ECG electrodes on the skin and displayed upon the screen of an oscilloscope with fast time base. *Lower trace.* Stable pacing from an external ventricular triggered pacemaker is achieved via an endocardial electrode. Oscilloscopic display shows that the stimulus artifact seen on the ECG is made up of 2 almost simultaneous impulses. The first is due to the implanted pacemaker, the second is due to the external unit which is triggered in less than 0.5 msec. It is this second impulse which paces the heart.

due to the second impulse (from the implanted unit). The rate setting of the ventricular-triggered pacemaker is not at all critical and the two impulses are virtually synchronous (Fig. 2) so that the ECG is not distorted by a second impulse. It is usually possible to tell from the shape of the QRS-T complex whether contraction was initiated by the implanted or the external pacemaker. This may be helpful in assessing results of treatment of exit block, and is a further slight advantage of the ventricular triggered over the demand pacemaker in this situation.

Whichever method is chosen stable pacing can be rapidly achieved and since the emergency situation is then controlled a decision as to whether the implanted pacemaker need be replaced or whether exit block can be treated with steroids can be taken on the basis of the usual clinical features.

Implanted variable rate pacemakers. If the failing implanted unit is itself of the noncompetitive type (i.e. atrial triggered, ventricular triggered, or demand) the situation is more complicated. If the implanted pacemaker will sense an electrical impulse delivered via the transvenous electrode it is recommended that temporary management be carried out with the standby rate of an external pacemaker set faster than both the spontaneous cardiac rhythm and the standby rate of the implanted unit. An implanted demand unit will then be totally inhibited. An implanted atrial-triggered or ventricular triggered unit will "lock on" to the rate of the external pacemaker. In both cases the heart will be paced by the external pacemaker without interference from the implanted unit.

A simple fixed-rate asynchronous external pacemaker can be used under these circumstances without competition since

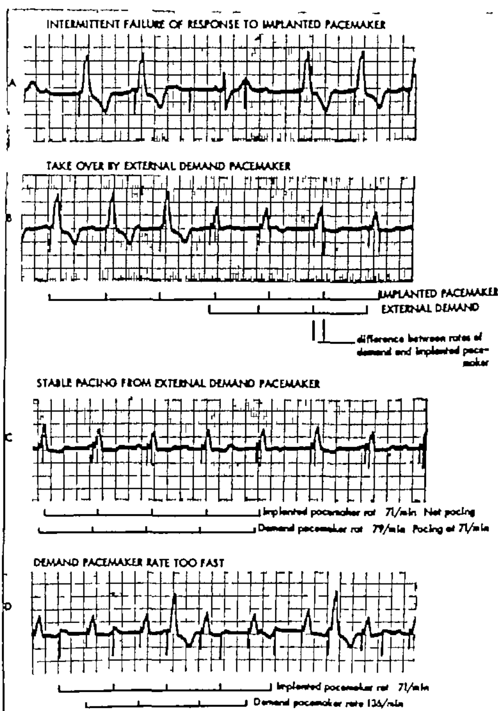
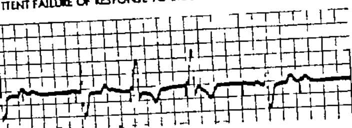


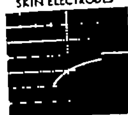
Fig *1* 1 The third and fourth impulses fail to produc cardiac cont action. The fourth impulse falls during the vulnerable period of a pontaneou beat *B* The first 3 be ts are in response to mpulses from an impla ted pacemaker The subsequent beat are caused by a temporary external demand pacemaker *C* The demand pacemaker is recycled from the ineffect timulu delivered by the impla ted nit Faci g is due to the demand pacemaker but the rate is that of the implanted unit. *D* Irregular rhythm, including tim lation during vulnerable period (i.e second mpulse from the mpla ted pacemak r) when the t of the demand pacemaker is set too fast

the heart the result will be stable pacing at the rate of the implanted pacemaker with out competitive rhythms. It should be noted that the standby rate of a demand pacemaker must be set *faster* than that of the implanted unit but that of a ventricu lar triggered pacemaker must be set *slower* The setting of the demand pacemaker is more critical since the rate must be only slightly faster th n that of the internal unit if satisfactory control is to be achieved without additional distortion of the ECG

…TTENT FAILURE OF RESPONSE TO IMPLANTED PACEMAKER

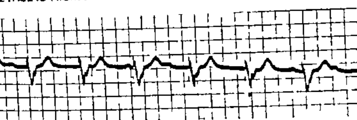


STIMULUS DETECTED FROM SKIN ELECTRODES



1 0 msec

…E PACING FROM EXTERNAL TRIGGERED PACEMAKER



2 STIMULI DETECTED FROM SKIN ELECTRODES



1 0 msec

…ig 2. *Upper trace:* The second impulse falls during the vulnerable period of the first (spontaneous) beat The impulse is detected from ECG electrodes on the skin and displayed upon the screen of an oscilloscope with th… fast time base. *Lower trace:* Stable pacing from an external ventricular-triggered pacemaker is achieved via an endocardial electrode. Oscilloscope display shows that the stimulus artifact seen on the ECG is made up of 2 almost simultaneous impulses. The first is due to the implanted pacemaker the second is due to the external unit which is triggered in less than 0 5 msec It is this second impulse which paces the heart

due to the second impulse (from the implanted unit) The rate setting of the ventricular triggered pacemaker is not at all critical and the two impulses are virtually synchronous (Fig 2) so that the ECG is not distorted by a second impulse It is usually possible to tell from the shape of the QRS-T complex whether contraction was initiated by the implanted or the external pacemaker This may be helpful in assessing results of treatment of exit block, and is a further slight advantage of the ventricular triggered over the demand pacemaker in this situation.

Whichever method is chosen stable pacing can be rapidly achieved and since the emergency situation is then controlled a decision as to whether the implanted pacemaker need be replaced or whether exit block can be treated with steriods can be taken on the basis of the usual clinical features.

Implanted variable rate pacemakers If the failing implanted unit is itself of the noncompetitive type (i e atrial-triggered ventricular triggered or demand) the situation is more complicated If the implanted pacemaker will sense an electrical impulse delivered via the transvenous electrode it is recommended that temporary management be carried out with the standby rate of an external pacemaker set faster than both the spontaneous cardiac rhythm and the stand by rate of the implanted unit. An implanted demand unit will then be totally inhibited. An implanted atrial-triggered or ventricular triggered unit will "lock on" to the rate of the external pacemaker In both cases the heart will be paced by the external pacemaker without interference from the implanted unit.

A simple fixed-rate asynchronous external pacemaker can be used under these circumstances without competition since

spontaneous beats are suppressed by the rapid pacing rate. It is preferable however for the temporary pacemaker to be non competitive (either demand or ventricular triggered) in case ectopic beats occur spontaneously

If the implanted noncompetitive pacemaker will not respond to the stimulus from an external unit the management is as for an asynchronous fixed rate unit as described previously

ERRATIC STIMULI FROM IMPLANTED UNIT In this situation emergency replacement of the implanted pacemaker is indicated since total failure may occur at any time. This may take the form of either a runaway pacemaker or complete cessation of function Temporary management is best carried out with an external ventricular triggered pacemaker not a demand pacemaker Both types will pace the heart if the implanted unit stops but the demand pacemaker will probably be completely inhibited if the implanted pacemaker runs fast.

Ventricular fibrillation may result from a runaway pacemaker if the heart responds to each stimulus. Alternatively the output energy of the implanted unit may fall if the rate becomes very fast so that the heart ceases to follow the pacemaker and ventricular asystole occurs. It is possible in either case for the temporary external pacemaker to detect and respond to the stimuli from the failing implanted unit. In this case an external ventricular triggered pacemaker will pace the heart at some preset upper limit and will not follow the tachycardia of the implanted unit. The upper limit of pacing often depends upon the setting of the pacemaker standby rate but a physiologically safe maximum pacing rate is incorporated into the design of all commercially available apparatus so that the heart cannot be driven too fast.

The rate settings suitable for each situation and type of pacemaker are shown in the table. The ventricular triggered type of external temporary pacemaker is simpler to use and is safer if the implanted pacemaker rate becomes faster and so this type should be used if possible.

If an adjustable ventricular triggered pacemaker is not available it may be possible to use a unit intended for implantation. Four such pacemakers are at present available (Biotronik IRP3 Cordis Ectocor Elema E M 153 and Sorin) and all are satisfactory for emergency cases as described here The limiting factor will be the standby rate of the available examples in comparison to that of the implanted failing pacemaker It is preferable to use a demand pacemaker with a rate correctly set than a ventricular triggered unit with an incorrect standby rate.

Summary and conclusions

The temporary management of patients when an implanted pacemaker fails to drive the heart but continues to produce stimuli is described

An endocardial electrode is passed transvenously and an external noncompetitive pacemaker used The rate settings of this pacemaker are critical and are described for different situations.

The ventricular triggered type of external pacemaker is easier to use and slightly safer than the demand type under these circumstances.

Transient electrocardiographic changes simulating myocardial infarction during open heart surgery

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The occurrence of transitory abnormal Q waves and other electrocardiographic abnormalities suggestive of acute myocardial infarction in patients undergoing open-heart surgery is reported In some patients these changes appeared during cross-clamping of the aorta and in others during the initiation of extracorporeal circulation. The disappearance of the abnormal Q waves and the other changes shortly after restoration of normal coronary flow indicate that these Q waves were transient and not due to permanent myocardial damage.

Abnormal Q waves have generally been considered to indicate either myocardial infarction or replacement of the myocardium by nonpolarizable tissue, such as amyloid sarcoid, fibrotic tissue, or metastatic infiltrates. This concept has recently been challenged by the appearance and disappearance of abnormal Q waves in a variety of clinical[1-[illegible]] and experimental conditions[[illegible]]

Method

Thirty patients were monitored electrocardiographically before, during and after the institution of extracorporeal circulation with or without occlusion of the aorta and coronary perfusion Leads I II III aV_R, aV_L, and aV_F were recorded. In some patients, Lead V_4 was also taken.

Electrocardiograms were taken before thoracotomy after pericardiotomy and after institution of extracorporeal circulation Tracings were also recorded following occlusion of the aorta, during coronary perfusion and at frequent intervals after the termination of these procedures. In all patients extracorporeal circulation was maintained with a Bentley bubble oxygenator and an American Optical pump with DeBakey roller type pump heads primed with blood. Flow rates ranged from 4 000 to 5 000 c.c. per minute at a temperature of 38° In 5 patients, the arteries were perfused by a separate system using a calibrated roller pump. The pressure was continuously monitored and kept below 350 mm. Hg the total flow was maintained at about 125 c.c. per minute in the right and 250 c.c. per minute in the left coronary artery The indwelling coronary catheters were of the Mayo-tip type (rubber tire for the left coronary artery balloon tip type

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Table I Pertinent clinical and operative data of patients who exhibited Q waves and/or ST T-wave changes

Patient	Sex	Age (yr)	Diagnosis	Operation	Aorta clamped	Coronary hypothermia	Coronary arteries	Postoperative complications	Comments
1	M	55	RHD MS	Mitral commissurotomy	No	No	Normal	—	
2	F	55	RHD MS AI	Mitral commissurotomy	Yes	No	Normal	—	
3	F	14	A V communis, MI pulmonary hypertension	Repair of defect	No	No	Normal	—	
4	F	60	MI 2° to ruptured chordae tendinae	Mitral valvuloplasty repair of chordae closure of foramen ovale	No	No	Normal	—	Previous thyroidectomy
5	M	43	RHD AS	S-E valve	Yes	Yes 28° C	Calcification and stenosis of LAD dominant right coronary system (coronary angiography)	—	Angina pectoris 3 months left coronary cannula unstable, held by hand isoproterenol infusion at end of procedure
6	M	37	RHD AS	S-E valve	Yes	No	Normal	—	Syncopal episodes post necrotic cirrhosis
7	M	35	RHD MS, recurrent AI mild	Mitral commissurotomy	No	No	Irregularities in both arteries (aortic root angiogram)	Recurrent ventricular tachycardia	
8	M	34	RHD AS MI	Aortic valve replacement mitral valve annuloplasty	Yes	Yes	Normal	Repeated episodes of ventricular tachycardia	
9	M	43	RHD MS AI	Mitral commissurotomy	Yes (2 min.)	No	Normal	Post-op psychosis	
10	M	42	RHD AS	S-E valve	Yes	Yes 28° C	Thickening and beading of left main and circumflex arteries right coronary artery normal	—	Diabetes mellitus
11	F	44	RHD MS	Mitral commissurotomy	Yes	No	Normal	DWMI 4 hr post op. (?) thrombophlebitis 16 days post-op.	Prior talcum poudrage

Abbreviations F Female M, male RHD, rheumatic heart disease MS, mitral stenosis MI, mitral insufficiency; AS, aortic stenosis; AI, aortic insufficiency S-E, Starr Edwards valve installment DWMI, diaphragmatic wall myocardial infarction

Table II. Contour of QRS complexes before and during extracorporeal circulation

Patient	Onset of changes*	Rhythm	I	II	III	V	V_L	V_F	Frontal axis (degrees)
1	10 min.	NSR		ST	ST		ST	ST	No change
2	Control	NSR	R	R	R	qR	Qr	R	+110
	7 min. (after aortic clamping)		QS, 0.01 sec. ST 2 mm.	R ST 3 mm	R ST 10 mm.	R ST	QS, 0.04 sec. ST	rSr ST	+130
3	Control	NSR	Rs	qR	qR	rS	rS	qR	
	Continuous tracing 5-8 min		R Qr 0.07 sec. ST						
	10 min.	VT							
4	Control	AF	Rs	qR	qR	rS	rS	qR	+ 70
	3 min.						QS, 0.08 sec QS	R	+110
	12 min		QS, 0.06 sec ST 3 mm.	R ST 3 mm.	R ST 3 mm	Q ST 3 mm.	ST 1 mm.		
	15 min.	VT							
5	Control	NSR	R	R	rSR	QS	qR	R	+ 30
	10 min. after coronary perfusion		Q 0.04 sec. ST	qR ST	qR ST	qR	Q, 0.04 sec. ST	qR ST	—
	2 min. after cooling		ST	Qr ST	ST		ST	ST	
6	Control	NSR	R	Rs	R	Qr	rS	qR	+ 30
	60 sec.		Rs	QS 0.08 sec ST	QS, 0.08 sec ST	rSr'	R ST	Qr ST	− 45
	2 min.		rS, ST	QS, ST	QS, ST	rsR ST	r ST	QS, ST	
7	Control	NSR	rS	R	qR	Qr	rS	qR	+110
	17 min.	AF	ST	ST 10 mm.	ST 10 mm.	rS	ST 5 mm.	ST 8 mm.	
8	Control	NSR	qR	Rs	qR	rS	rsR	R	+ 40
	15 min. after cooling of coronary blood		QS, 0.08 sec.	R	R	rsR	QS, 0.08 sec.	R	+120
9	Control	AF	R	R	RS	QS	rSR	R	+ 45
	2 min.		QS, 0.04 and 0.06 sec	R	qR	rS	QS	R	+100
10	Control	NSR	R	qR	QR 0.04 sec.	rS	R	qR	+ 25
	2 min		R	qR	QS, 0.05 sec.			QS, 0.08 sec.	
	7 min		QS 0.08 sec ST	qR ST	qR ST	rSr ST	QS, 0.08 sec. ST	qR ST	+110
11	Control	NSR-AF	qRs	R	rS	rS	qR	qrS	+ 10
	3-5 min.		ST 3 mm.	ST 10 mm	ST 10 mm.	ST 3 mm.	ST 3 mm	ST 10 mm.	+ 10

NSR, Normal sinus rhythm; AF, atrial fibrillation; VT, ventricular tachycardia.
*Except when indicated, column no. 2 refers to the time interval between institution of extracorporeal circulation and onset of QRS changes. In Patients 1, 7, and 11 only ST-T changes developed.
All QRS complexes reverted to their normal appearance after cessation of bypass. In Patient 5, reversion to normal appearance occurred spontaneously during hypothermia.

for the right coronary artery) In 3 patients Nos. 5 8 and 10 the temperature of the coronary blood was lowered to 28° C Except in Patient 5 the coronary ostia accepted the catheters easily and coronary perfusion was maintained without difficulty The blood pH pCO_2, pO_2, and electrolytes were kept within normal range. In none was a left ventriculotomy performed The ventricular vent consisted of a 20 gauge needle inserted into the apex of the left ventricle Its insertion produced no electrocardiographic abnormalities

Results

Serial electrocardiographic changes developed in 11 patients. Age sex and other pertinent data in these patients are summarized in Tables I and II Nine of the 11 were regarded as cases of rheumatic heart disease. Four patients Nos. 5 6 8 and 10 had aortic stenosis, one had associated mitral insufficiency The other five Nos. 1 2 7 9 and 11 had mitral stenosis Two of the five 7 and 9 also had aortic insufficiency One patient No 3 had congenital heart disease and one No 4 had mitral insufficiency secondary to spontaneous rupture of the chordae tendineae Seven were men and 4 were women The ages varied between 14 and 60 years

The electrocardiographic changes occurred within 1 to 17 minutes after institution of extracorporeal circulation in 8 patients. In Patients 2 and 5 the changes were noted after occlusion of the aorta both before and after cannulation of the coronary arteries. In Patient 8 the abnormalities developed 15 minutes after perfusion of the coronary arteries with cooled blood

In Patients 6 and 10 Q waves or QS complexes, varying in duration between 0 04 and 0 08 sec. appeared in Leads II III and aV_F similar to those observed in acute inferior wall myocardial infarction (Figs. 1 and 2) One of these No 10 also had elevation of the S-T segments in Leads II III and aV_F In Patient 10 several minutes following the development of a pattern consistent with inferior wall infarction a supraventricular tachycardia occurred Q waves then appeared in Leads I and aV_L resembling the pattern of acute anterior wall myocardial infarction In 6 patients Nos. 2 3 4 5 8 and 9 abnormal Q waves developed in Leads I and aV_L suggestive of anterior wall infarction. In 3 patients, Nos. 1 7 and 11 significant S-T segment elevations greater than 2 mm. appeared in Leads II III and aV_F suggestive of inferior wall myocardial injury but Q waves did not develop. In all 11 the abnormalities subsided within 1 to 5 minutes after the cessation of extracorporeal circulation Serial enzymes were not taken

The postoperative course was uncomplicated in all except 3 patients. Several episodes of ventricular tachycardia occurred in Patient 8 Patient 9 had a postoperative psychotic episode. Patient 5 required isoproterenol infusion before satisfactory myocardial contractility could be achieved at the end of surgery All 3 recovered

Discussion

Bayley and La Due[14] demonstrated that abnormal Q waves could be produced experimentally in the absence of myocardial infarction This finding has been confirmed by others. Gross and associates[15] attributed transient abnormal Q waves to reversible electrophysiologic inertness of areas of the myocardium DePasquale and co-workers[1] referred to this phenomenon as transient electrical silence They rely on Hoffman and Suckling's[16] work for the dynamics. Transient Q waves have also been reported in clinical situations such as angina pectoris[1,2] coronary insufficiency[1-4] asthma[6] uremia with hyperkalemia[7] hypoglycemia[8] shock[8,9] tachycardia[10] phosphorus poisoning[11] and pancreatitis.[12] The occurrence of pathological Q waves has also been demonstrated in pancreatitis.[13]

The present report demonstrates that transient abnormal Q waves also occur during the institution of extracorporeal circulation with or without cross-clamping of the aorta and coronary perfusion and disappear promptly after cessation of these procedures The rapid disappearance of these abnormal Q waves indicates that they were caused by temporary alterations of cellular electrical activity and not by irreversible damage of myocardial cells.

Several mechanisms may have caused the abnormal Q waves in our patients.

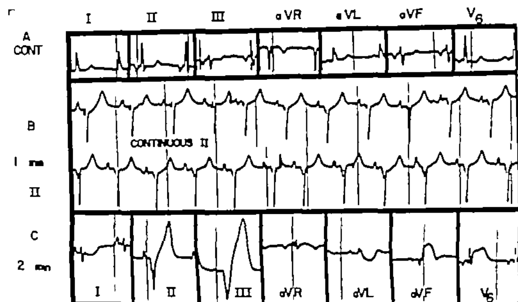


Fig. 1A. ECG of Patient 6. (*A*) Control tracing after thoracotomy. Note inverted P waves in Leads II, III, V and V and subsequent changes in P waves. (*B*) Continuous Lead II one minute after onset of extracorporeal circulation showing a small Q wave followed by small and progressing to slurred QS complexes. (*C*) Inferior wall myocardial infarction pattern present two minutes after onset of extracorporeal circulation, QS complex in Leads II, III and V peaking of T waves in II and III, S-T segment elevation, and reciprocal S-T depression in I and V_L.

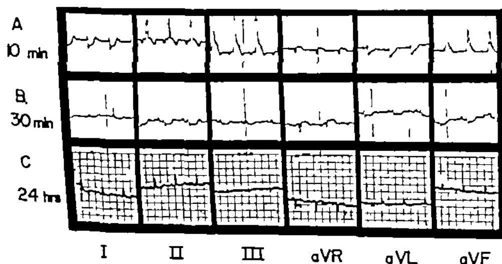


Fig. 1B. ECG of Patient 6. (*A*) Ten minutes, (*B*) 30 minutes, and (*C*) 24 hours after cessation of extracorporeal circulation. The pattern of inferior wall myocardial infarction has disappeared, and the ECG has reverted to normal.

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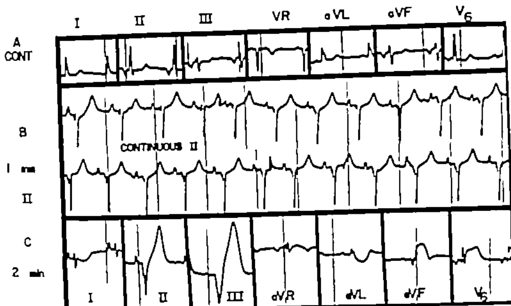


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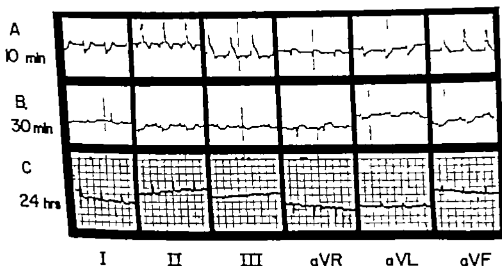


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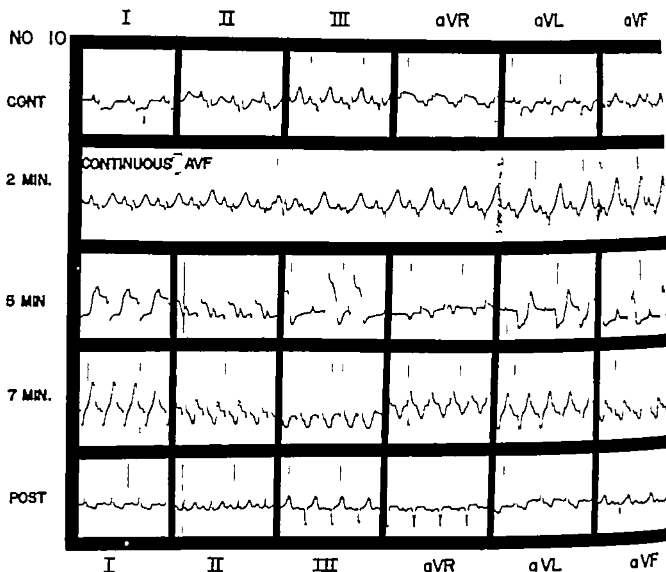


Fig 3 ECGs of Patient 10. *Top line* Control tracing obtained after thoracotomy Small q waves in Leads II III and aV_F S-T-segment depression in Lead I and aV_L, and S-T elevation in Leads aV_R and III *Second line* A continuous Lead aV_F obtained 2 minutes after onset of extracorporeal circulation QS complexes gradually lose positive components and become deep, slurred QS complexes while the T waves gradually become more peaked these changes suggest inferior wall myocardial infarct. *Third line* The pattern previously observed has changed 5 minutes after onset of bypass and there is now a tall R wave in Leads II III and aV_F associated with marked elevation of the S-T segments. Leads I and aV_L now show predominantly negative complexes (QRS in I and RS in aV_L) with marked S-T segment depression First and second degree A V block and premature beats are now present. *Fourth line* Seven minutes after onset of bypass, the pattern of anterior wall myocardial infarction is evident—QS in Leads I and aV_L with peaking of the T waves. The rhythm is supraventricular tachycardia rate 150 beats per minute. *Bottom line* Disappearance of the anterior wall infarct pattern after cessation of extracorporeal circulation Lead III and aV_F have rS complexes.

These are

1 Injury to the coronary arteries during cannulation.[17] However if injury to the coronary arteries were the cause the abnormalities should have persisted over a protracted period

2. Another possible mechanism for the transient development of abnormal Q waves[18] is selective ischemia and hypoxia of the ventricular myocardium This view is supported by known coronary artery disease in 3 of the patients Nos. 5 7 and 10 However localized ischemia may occur in the absence of coronary artery disease Hypoxia and ischemia may cause failure of a portion of the myocardium to polarize and depolarize leading to electrophysiologic inertness or electrical silence of this area. Restoration of normal blood supply to this portion of the myocardium may be followed by normal polarization and depolarization

3 Another mechanism for the development of abnormal Q waves may be due to contraction of muscle sphincters in capillaries. These sphincters are innervated and respond to neurohormonal pharmacologic agents, notably catecholamines.[14-20] James[21] feels that these sphincters may constrict in certain clinical situations and lead to arteriovenous shunting of blood at the precapillary level and thereby to myocardial ischemia. Precapillary shunting has not been demonstrated as a cause of myocardial infarction. Such a mechanism might conceivably operate during extracorporeal circulation, metabolic imbalance, hypotension, hypoglycemia, and tachycardia. In all these situations, the level of circulating catecholamines is usually increased. Although blood flow would remain at an acceptable level in the large coronary arteries or coronary cannulae, neurohumoral influences could produce closure of the precapillary sphincters and result in shunting of blood away from certain areas of the myocardium and produce abnormal electrocardiograms.

4. Localized metabolic disturbances and electrolyte imbalance notably hyperkalemia, may alter ventricular depolarization. Hemolysis during extracorporeal circulation may increase extracellular potassium concentration in the heart. Hypoxia predisposes to potassium efflux from cardiac cells.[22] Localized hyperkalemia might exist although serum electrolyte determinations during cardiac surgery would not detect such local accumulations of potassium in the walls of the ventricular capillaries.

Localized alterations in the relation of extracellular to intracellular potassium with hypoxia may induce marked changes in the electrical activity of the cells in the affected areas. Increased extracellular potassium concentration decreases the resting cell membrane potential and the velocity and amplitude of spontaneous depolarization of ventricular muscle of intact hearts[14,23-27] and of the Purkinje fibers.[14,28] Localized hypoxia and hyperkalemia when severe, may lead to decreased electrical activity or even to electrical silence of the affected fibers. Such changes could be reflected in the electrocardiogram by a shift of the mean vector away from the electrically malfunctioning areas. Hypoxia also increases the rate of spontaneous diastolic depolarization (Phase 4) in the Purkinje fibers.[17,23] Enhanced Phase 4 depolarization in the Purkinje fibers causes a variety of disturbances of conduction and responsiveness ranging from simple slowing of conduction to decremental unidirectional and bidirectional block and even unexcitability.[29]

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When abnormal Q waves and/or ST and T wave abnormalities develop during open heart surgery the diagnosis of myocardial ischemia or infarction is suggested. When they persist, serial electrocardiograms (ECG's) must be taken to exclude a diagnosis of recent myocardial damage. The evaluation of serum glutamic oxalacetic acid transaminase and lactic dehydrogenase tests would be difficult since there are many causes of abnormalities of these enzymes in these patients. Specific cardiac isoenzymes would be useful in this circumstance. The disappearance of the ECG abnormalities when a patient was taken off the pump indicates that permanent myocardial damage had not occurred.

The transient nature of the ECG changes and their rapid disappearance during or shortly after operation and the shift in minutes from a pattern suggestive of myocardial infarction in one area to another are evidence against the occurrence of myocardial infarction. These electrocardiographic abnormalities are similar to the transitory abnormal Q waves occurring in other clinical conditions and are best considered manifestations of reversible electrophysiologic aberration or electrical silence in localized areas of the ventricular myocardium.

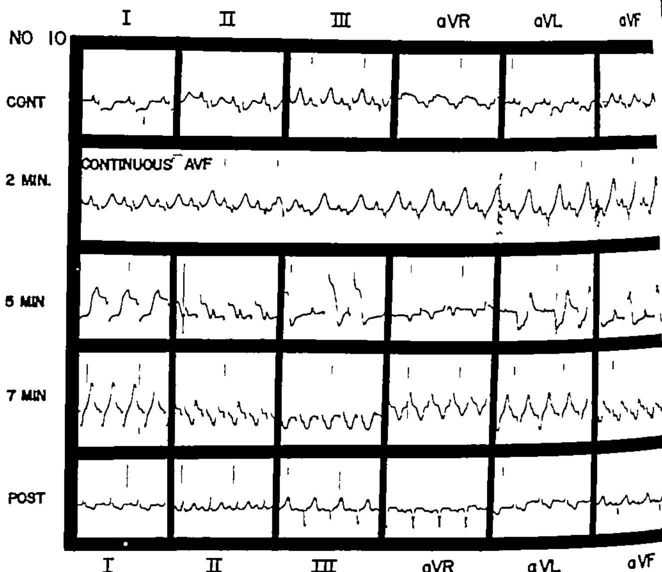


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5. Another possible cause of the electrocardiographic changes is hypothermia. This mechanism is suggested in Patient 8. At the level of hypothermia to which the patients were exposed (+8° C) little occurs to the resting membrane potential of the Purkinje and ventricular fibers, but repolarization is prolonged because of a decrease in the slope of Phase 2.[30] Prolonged duration of repolarization of either Purkinje or ventricular fibers would be associated with prolonged refractoriness in these fibers and result in the propagation of the electrical forces through aberrant pathways of conduction and subsequent alteration of the QRS complex.

When abnormal Q waves and/or ST and T wave abnormalities develop during open-heart surgery the diagnosis of myocardial ischemia or infarction is suggested. When they persist serial electrocardiograms (ECG's) must be taken to exclude a diagnosis of recent myocardial damage. The evaluation of serum glutamic oxalacetic acid transaminase and lactic dehydrogenase tests would be difficult since there are many causes of abnormalities of these enzymes in these patients. Specific cardiac isoenzymes would be useful in this circumstance. The disappearance of the ECG abnormalities when a patient was taken off the pump indicates that permanent myocardial damage had not occurred.

The transient nature of the ECG changes and their rapid disappearance during or shortly after operation and the shift in minutes from a pattern suggestive of myocardial infarction in one area to another are evidence against the occurrence of myocardial infarction. These electrocardiographic abnormalities are similar to the transitory abnormal Q waves occurring in other clinical conditions and are best considered manifestations of reversible electrophysiologic aberration or electrical silence in localized areas of the ventricular myocardium.

Summary

Eleven patients are described in whom an electrocardiographic pattern consistent with myocardial infarction appeared transiently during open heart surgery Eight had abnormal Q waves, the other 3 had only ST and T changes The rapid disappearance of the electrocardiographic abnormalities during or shortly after cessation of extracorporeal bypass suggests that the changes were due to temporary alterations in ventricular depolarization and not to permanent myocardial damage. The possible mechanisms responsible for these alterations are discussed

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Evaluating coronary care units

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Since the early description of coronary care units (CCU's) in 1963,[1-4] the number of hospitals which have opened such units has increased rapidly. This was done with the expectation that death due to acute myocardial infarction would be substantially reduced. Early estimates of the potential magnitude of this reduction were that as many as 100,000 lives would be saved each year if all hospitals in the United States had units. In 1965 the Heart Disease and Stroke Control Program undertook a study attempting to quantitate the effect of CCU's on myocardial infarction mortality rates among many hospitals. Analysis of the data has been performed and appropriate differences between observed and expected fatality rates were tested for significance. (Earlier results, without study of significance, have been presented elsewhere.[5])

Methods

An attempt was made to collect data on consecutive patients with the final diagnosis of definite acute myocardial infarction from each of thirteen hospitals. All hospitals had a coronary care unit staffed by specially trained nurses, 24 hour physician coverage in the hospital, and ready availability of an emergency cardiopulmonary resuscitation team.

Identical instructions for data collection were given to each participating institution. A 2 page form was completed in each hospital for patients treated before the CCU opened (prior group) and for patients treated entirely in regular care after the CCU opened (concurrent regular care group). In most hospitals, this same form was used for CCU treated patients; a more detailed form was used for the CCU patients in several of the hospitals. Patients dying after transfer from the CCU were considered members of the CCU group and their deaths were counted as CCU-patient deaths. Prior group data were collected retrospectively; regular care and CCU groups were studied prospectively.

At this time sufficient data to permit a study to be made of the effectiveness of the CCU when compared to a group of patients treated in the same hospital before the CCU opened have been obtained from only five hospitals. The unit and hospital sizes of these are summarized in Table I. All hospitals in this study are general hospitals. B and C are university

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teaching hospitals the others are community hospitals. The bed size of the unit in Hospital E increased from 4 to 10 beds during the study

The other eight hospitals had various reporting inadequacies. Usually the inadequacy occurred in cases in the control (non-CCU) groups and consisted either of incomplete data on individual patients or periods of time during which no records were available.

Since the study was designed to determine the effect of a coronary care unit in different hospital settings, any factor which might have altered patient care in a given hospital such as the number of electrocardiograms taken laboratory tests, and drugs used was not standardized All cases were reviewed by the senior cardiologist of the individual hospital and he passed his criteria for the diagnosis of a definite acute myocardial infarction Four categories of criteria were employed ECG enzymes clinical history and autopsy Over 90 per cent of all the patients satisfied criteria in more than one category Physical examination data were interpreted in the same way in each hospital to determine the presence of shock or congestive heart failure at the time of admission Thus, definitions were uniform within a given hospital but may have varied among different hospitals. For this reason data from the five hospitals are presented individually

The fatality rate of definite myocardial infarction patients treated in a CCU was compared with that of patients treated in the same hospital before the unit opened One hospital provided enough data on consecutive concurrent regular care patients to allow a comparison of this group to the CCU In addition the concurrent regular care and the CCU groups from this hospital were combined to give the total hospital experience after the CCU was opened and this was compared with the prior to-CCU experience

Age-severity adjusted fatality rates were calculated for each of the five hospitals. Each prior CCU and regular care group was separated by age into two subgroups those under 60 and those 60 and over Hospital admission clinical status was used to subdivide each age group into two severity classes complicated and uncomplicated Complications include cardiac arrest on or before admission clinical shock hypotension without clinical shock (systolic blood pressure less than 90 mm Hg) and congestive heart failure. The specific fatality rate in each of the resulting four age-severity subgroups was determined Significance of the difference between control and CCU age-severity specific fatality rates was calculated by a one-tailed chi square test except when the number of cases in any cell was less than 5 in these circumstances, Fisher's exact method was used to calculate significance[1]

By multiplying the age-severity specific fatality rate of each control subgroup by the number of patients in the corresponding age-severity CCU subgroup the expected deaths for the latter was determined It was then possible to compare the sum of actual deaths observed after the CCU was organized with the adjusted total expected to occur had the prior to CCU fatality experience still been in effect Significance between observed and expected adjusted fatality rates was determined (see Appendix) This method was also used in comparing the CCU with regular care and the combined after CCU group with the prior group for Hospital A.

Twenty-one patients from all five hospitals were deleted from the study because the hospitals were unable to ascertain an exact age Eight of these were in the prior group including 3 deaths and 13 in the CCU group including 4 deaths.

About 15 per cent of the CCU treated patients were not admitted directly to the CCU and received initial treatment in other areas of the hospital Many of these late admissions were patients whose

Table I Description of hospitals used in detailed analysis

Hospital	CCU beds	Hospital beds
A	5	250
B	2	700
C	2	670
D	4	450
E	4 to 10	350

condition worsened prior to CCU admission and probably were admitted only because of this. Therefore, for comparison of CCU with prior or regular care groups, data on all patients who were delayed more than six hours between hospital admission and CCU admission were arbitrarily deleted from the CCU treated group. The unadjusted fatality rate of these patients was 31 per cent. However these patients were included in the combined regular care and CCU group in the one hospital in which the entire hospital experience before and after CCU was compared.

Table II Crude fatality rates among CCU-treated MI patients

Hospitals	*MI patients*	*Fatality rates (%)*
1	272	16.5
2	358	20.7
3-A	626	20.9
4	310	21.3
5	345	23.5
6	405	24.7
7-E	247	25.1
8	367	26.4
9-C*	323	26.9
10-D*	204	27.0
11	196	28.1
12	192	28.1
13-B	150	31.3
Total	3 995	23.9

*Included in subsequent analyses of age-severity. Adjusted rates

Results

The results are summarized in Tables II to VIII. The data are presented in different ways to demonstrate how the method of analysis can influence results.

Table II shows the crude fatality rates for all myocardial infarction patients treated at any time during hospitalization in a CCU in all thirteen hospitals. The asterisked hospitals are those used in this report. There is a discrepancy in total CCU patients listed in this table and subsequent tables for these hospitals because in subsequent analysis, delayed CCU admissions, as noted above, were excluded.

In Table III data from one hospital is presented to show the results of alternative subgroup comparison. The unadjusted mortality figures show a lower mortality rate in the CCU group (37.5 vs. 26.7 per cent) but the difference is not statistically significant ($p > 0.05$). When the sample populations are divided according to age, the CCU appears effective only in the age 60 and over subgroup although the difference is still not significant. When the samples are divided according to admission severity a mortality reduction is noted in both subgroups and the results are statistically significant. When classified by both age and severity the reduction in the mor

Table III Subgroup comparisons in Hospital B

Group	*Prior*		*CCU*	
	No. of patients	*Mortality rate*	*No. of patients*	*Mortality rate*
Crude	184	37.5	116	26.7
Under 60	48	20.8	66	22.7
60 and over	136	43.4	50	32.0
Uncomplicated	131	29.8	51	9.8
Complicated	53	56.6	65	40.0†
Under 60, uncomp.	37	13.5	35	5.7
Under 60, comp.	11	45.5	31	41.9
60 and over uncomp.	94	36.2	16	18.7
60 and over comp.	42	59.5	34	38.2†

Legend: Uncomp. = Uncomplicated, comp. = complicated.
*$p < 0.05$.
†$p < 0.01$.

Table IV *Subgroup specific comparisons*

Hospital	*Subgroup*	*Prior*		*CCU*	
		No of patients	*Mortality rate*	*No of patients*	*Mortality rate*
A	Under 60, uncomp	116	6.9	213	5.7
	Under 60 comp.	19	42.1	66	22.7
	60 and over uncomp.	91	31.9	146	20.5
	60 and over comp.	33	69.6	123	38.2†
C	Under 60 uncomp	57	24.6	101	11.9‡
	Under 60 comp.	46	32.6	74	36.5
	60 and over uncomp.	51	27.5	45	11.1‡
	60 and over comp.	76	48.7	58	48.3
D	Under 60 uncomp.	70	12.9	4	50.0
	Under 60 comp.	4	50.0	4	25.0
	60 and over uncomp	88	33.0	94	29.8
	60 and over comp	12	50.0	19	47.4
E	Under 60 uncomp	82	8.5	61	9.8
	Under 60 comp.	7	42.9	11	63.6
	60 and over uncomp	73	30.1	57	24.6
	60 and over comp.	17	47.1	32	53.1

Uncomp. = Uncomplicated; comp. = complicated.
*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.02$

Table V *Over-all efficacy of the CCU*

Hospital	*No. of CCU patients*	*Total observed CCU deaths*	*Total "expected" CCU deaths**	*% Change*
A	548	104	147.7	−40†
B	116	31	44.9	−31‡
C	278	72	89.6	−20
D	175	46	50.0	− 8
E	161	44	42.2	+ 1

*Sum of deaths expected for each age-severity subgroup.
†$p < 0.01$.
‡$p < 0.05$.

tality rate in the CCU sample is significant only in the complicated age greater than 60 subgroup.

Table IV summarizes the age severity specific comparisons of prior and CCU patients for the other four hospitals. It can be noted from Tables III and IV that 15 out of the 20 age-severity specific comparisons show a lower fatality rate in the CCU patients although only 6 are statistically significant. Three of these 6 are in the one hospital which had the most patients.

The over-all age-severity adjusted expected CCU deaths are compared with actual observed CCU deaths in Table V. The impact of a CCU varied from significant benefit in Hospitals A and B to little or no benefit in Hospitals D and E.

The over-all results and significance levels for the one hospital from which complete regular care data was available are

Table VI *Concurrent regular care in Hospital A*

Comparison	*No. of patients in (b)*	*Observed deaths (b)*	*Adjusted deaths expected* from (a)†*	*% Change in (b)*
(a) Current regular care versus (b) CCU	548	104	142.6	−27‡
(a) Prior series (b) Current regular care plus CCU	813	185	268	−31§

*Group (a) compared with Group (b).
†Sum of deaths "expected" for each age-severity subgroup based on data from (a).
‡p < 0.05.
§p < .01.

Table VII *Over-all efficacy of CCU in "good risk" patients*

Hospital	*No. of "good risk" CCU patients**	*Total observed CCU deaths*	*Total expected CCU deaths†*	*% Change*
A	438	52	101.8	−49‡
B	97	18	28.3	−36§
C	236	44	68.8	−33‡
D	163	40	40.6	0
E	135	26	26.2	0

*Patients without shock or prior cardiac arrest at time of admission.
†Sum of deaths expected for each age-severity subgroup.
‡p < 0.01.
§p < 0.05.

presented in Table VI. In the upper half of the table the actual CCU deaths are compared with age-severity adjusted deaths "expected" from concurrent regular care experience. In the lower half a significant change is noted in comparing the total hospital actual deaths after the introduction of the CCU with a time period before the CCU was opened. Thus, in this hospital the CCU was more effective than regular care and combined CCU-regular care was also improved over prior to-CCU experience.

The effect of selection of patient groups is illustrated in Table VII. "Poor risk" patients (those with shock or prior cardiac arrest at time of admission) have been excluded and the method for determining over-all effectiveness was applied to the remaining age-adjusted "good risk" group.

It should be noted that the CCU results of Hospital C are significant for "good risk" patients where the CCU improvement was not significant for the entire group (Table V).

Discussion

The variable effectiveness of a CCU found among the five hospitals studied is consistent with the variable results reported in the literature. Other studies have found the effect of CCU's on mortality rates to range from negligible change[1,4] to 50 per cent reduction. However some of the variability in previous reports can probably be ascribed to different methods of study design and statistical analysis, and to inconsistent definitions and inclusion criteria. To the extent that this study avoided these difficulties, the results can

Table IV Subgroup specific comparisons

Hospital	Subgroup	Prior: No. of patients	Prior: Mortality rate	CCU: No. of patients	CCU: Mortality rate
A	Under 60, uncomp.	116	6 9	13	5
	Under 60, comp.	19	4 1	66	[illegible]
	60 and over uncomp.	91	11 9	146	2.5*
	60 and over comp.	33	69 6	1 3	35 7
C	Under 60, uncomp.	57	4 6	101	11 9
	Under 60 comp.	46	3 6	4	6 5
	60 and over uncomp.	51	5	45	11 1
	60 and over comp.	6	45	58	48 3
D	Under 60, uncomp.	0	12 9	4	50 0
	Under 60, comp.	4	50 0	4	5 0
	60 and over uncomp.	58	33 0	94	29 8
	60 and over comp.	12	50 0	19	47 4
E	Under 60, uncomp.	8	5 5	61	9 8
	Under 60, comp.	7	4 9	11	63 6
	60 and over uncomp	3	30 1	5	4 6
	60 and over comp.	1	4 1	3	53 1

Uncomp. = Uncomplicated, comp. = complicated.
*p < 0.05.
†p < 0.01
‡p < 0.02.

Table V Over-all efficacy of the CCU

Hospital	No. of CCU patients	Total observed CCU deaths	Total "expected" CCU deaths*	% Change
A	548	104	14	−40†
B	116	31	44 9	−31‡
C	8		89 6	−0
D	1 5	46	50 0	− 8
E	161	44	4	+ 1

*Sum of deaths expected for each age-severity subgroup.
†p < 0.01.
‡p < 0.05.

tality rate in the CCU sample is significant only in the complicated-age greater than 60 subgroup.

Table IV summarizes the age-severity specific comparisons of prior and CCU patients for the other four hospitals. It can be noted from Tables III and IV that 15 out of the 20 age-severity specific comparisons show a lower fatality rate in the CCU patients although only 6 are statistically significant. Three of these 6 are in the one hospital which had the most patients.

The over-all age-severity adjusted "expected" CCU deaths are compared with actual observed CCU deaths in Table V. The impact of a CCU varied from significant benefit in Hospitals A and B to little or no benefit in Hospitals D and E.

The over-all results and significance levels for the one hospital from which complete regular care data was available are

Table VI. *Concurrent regular care in Hospital A*

Comparison	No. of patients in (b)	Observed deaths in (b)	Adjusted deaths "expected"* from (a)†	% Change in (b)
(a) Current regular care versus (b) CCU	548	104	142 6	−27‡
(a) Prior versus (b) Current regular care plus CCU	813	185	268	−31§

*Group (a) compared with Group (b).
†Sum of deaths "expected" for each age-severity subgroup based on data from (a).
‡p < 0 05
§p < 0 001.

Table VII *Over-all efficacy of CCU in "good risk patients*

Hospital	No. of good risk CCU patients*	Total observed CCU deaths	Total expected CCU deaths†	% Change
A	438	52	101 8	−49‡
B	97	18	28 3	−36§
C	236	46	68 8	−33‡
D	163	40	40 6	0
E	135	26	26 2	0

*Patients without shock or prior cardiac arrest at time of admission.
†Sum of deaths expected for each age-severity subgroup
‡p < 0.01.
§p < 0 05

presented in Table VI In the upper half of the table the actual CCU deaths are compared with age-severity adjusted deaths expected" from concurrent regular care experience In the lower half a significant change is noted in comparing the total hospital actual deaths after the introduction of the CCU with a time period before the CCU was opened. Thus, in this hospital the CCU was more effective than regular care and combined CCU-regular care was also improved over prior to-CCU experience

The effect of selection of patient groups is illustrated in Table VII Poor risk patients (those with shock or prior cardiac arrest at time of admission) have been excluded and the method for determining over all effectiveness was applied to the remaining age-adjusted good risk" group

It should be noted that the CCU results of Hospital C are significant for good risk patients where the CCU improvement was not significant for the entire group (Table V)

Discussion

The variable effectiveness of a CCU found among the five hospitals studied is consistent with the variable results reported in the literature. Other studies have found the effect of CCU s on mortality rates to range from negligible change[1-] to 50 per cent reduction. However some of the variability in previous reports can probably be ascribed to different methods of study design and statistical analysis, and to inconsistent definitions and inclusion criteria. To the extent that this study avoided these difficulties, the results can

be taken as evidence for a true variation in coronary care unit effectiveness.

Study design The prime requisite for an adequate evaluation of a method of treatment is a control group for comparison To ensure that comparison is valid both control and experimental groups should be stratified into appropriate subgroups of similar prognosis.[8]

Some studies on CCU s have not used control groups and have stressed descriptive material on the myocardial infarction patients.[9 10] The work of Schnur[11] can be used to point out the fallacy of comparing these reports with the standard 30 to 40 per cent mortality observed before CCU s. He studied four hospitals over a 10 year period and found the 10 year average fatality rates from each hospital varied from 10 to 52 per cent depending upon such factors as type of hospital and admission policies. In our study the prior group crude mortality ranged from 22 to 37 per cent.

Another approach to quantitating efficacy without a control group has been to derive an expected death rate for a CCU by adding cardiac arrest survivors to the actual deaths this assumes that the patients with cardiac arrest would probably have died without the unit[12 13] This method ignores the philosophy of arrhythmia prevention and considers only the results of treating the failures of arrhythmia prophylaxis. Furthermore survival from cardiac arrest due to myocardial infarction does occur outside of coronary care units.[13 14]

Three types of control populations have been used for comparison with CCU treated samples. One method has been to compare the mortality rate in a hospital with a CCU with the mortality experience in another hospital which does not have a CCU[14 15] Such comparisons require in addition to matched prognostic groups assumptions which are unlikely to be justifiable concerning identical admission criteria operating policies, facilities, and therapeutic philosophy

Some investigators have compared CCU results with data obtained from patients treated simultaneously on regular medical wards.[6,16] Our data from the one hospital in which it was tabulated shows CCU-treated patients to have a lower mortality rate. This method could come close to employing an ideal control group if regular care were uniformly defined and applied, if random allocation of patients into CCU and regular care were possible and if appropriate prognostic classifications were made. However it has not been possible in this or any other study to adequately insure uniformity in the regular care control group treatment of patients in this group may have occurred in locations ranging from an isolated private room with little observation to modified intensive care wards. In addition actual selection of patients for CCU care is unlikely to be random and factors such as bed availability the attending physician s attitude toward CCU s clinical appraisal of the need for CCU care and extra costs for CCU treatment could influence decisions.

The method of comparing the coronary care unit effectiveness with prior experience in the same hospital has been used by others.[3 7 16 17] The chief difficulty with this method is that the treatment occurred in a later time period than the control A number of other therapeutic measures were introduced at about the same time as the CCU such as liberal use of lidocaine, atropine and transvenous pacemakers. Accordingly it is very difficult to separate the discrete effect of a CCU from the impact of the other measures when comparisons are made with a time period when none of these existed However it should be pointed out that optimum use of the newer therapeutic procedures probably cannot be achieved without the close observation possible in an intensive care environment.

Further difficulties with a prior control group relate to the year to-year changes in hospital mortality statistics and the problem of nonuniformity of treatment Much of the difference in yearly mortality statistics can be minimized by prognostic stratification of CCU and control groups, but the possibility of bias is not entirely controlled

These considerations are in agreement with comments by others and lead to

one conclusion that it is probably not possible to arrange for an ideal control population in evaluating CCU's.[8,9] Use of a group of "prior to-CCU" patients for comparison seems to offer the closest approximation when diagnostic criteria are standardized and patients are classifiable on important variables affecting prognosis.

A totally different question from the effectiveness of a CCU per se relates to the effect of introducing a Unit as measured by the *total* hospital myocardial infarction (MI) case fatality rate. To answer this question requires analysis of all patients admitted to the hospital after the CCU opened regardless of whether or when they were in the CCU. The percentage of total MI admissions which are treated in the unit is a critical variable in this analysis. In addition the same limitations are present with this approach as with the comparison of prior and CCU care data discussed above. The data presented in Table VII demonstrate a positive result in one hospital in which most of the MI admissions were treated in the CCU.

Of the studies which have used control groups, prognostic stratification was sometimes neglected.[7,17] The prognostic heterogeneity of a sample of myocardial infarction patients was reconfirmed by data from all five hospitals. Table III shows how simple classification of a prior or CCU group by either age alone or severity alone can result in differences in mortality. Similar classification of the other four hospitals had the same effect.

Table III also emphasizes the importance of classifying experimental and control populations by prognosis. If the data from this hospital had been classified merely according to admission severity the efficacy of the CCU in that hospital would be confirmed. On the other hand if the data were classified solely according to age the results would not be significant. With both age and severity taken into account, a statistically significant conclusion can be drawn for only one of the subgroups. Nevertheless, Table V derived by using the method of determining expected deaths, indicates that the over-all age-severity adjusted results are significant at the 0.05 confidence level for this particular hospital.

Even when prognostic stratification is used different results can be obtained by considering only relatively "good risk" patients. Hospital C showed a significant improvement for CCU treatment of only "good risk" patients while the improvement for all CCU patients in this hospital was not confirmed statistically.

Other factors in addition to age and admission severity have been found to be important in predicting prognosis; however, there has been considerable disagreement in the literature concerning the identification of these factors and how much weight each should be given.[18-21] Further subdivision such as by history or laboratory results, was not undertaken in this study because of the small numbers which would have resulted. Such subdivision, of course, may have led to different results.

Statistical methods. Tests of statistical significance have rarely been used in reports comparing a CCU group with a control. Observations of large reductions in mortality rate unaccompanied by tests of statistical significance are uninterpretable. The method of comparing the CCU with a prior control group using age-severity adjustment and determining statistical significance has not previously been reported. However it should be emphasized that even with the large number of patients studied the method of adjustment for age and severity reduced the number of patients in each subcategory. As a result, the effect being measured must either be relatively large in order to be confirmed statistically or the number of patients studied must be very large in order to detect small differences.

Other sources of variation. The definition of complications employed in a study on patients with myocardial infarction can affect the final results. Table VIII shows the incidence of congestive heart failure and shock in each of the five hospitals. The incidence of congestive heart failure syndromes due to acute myocardial infarction reported in the literature has the same diversity as shown here. Sampson and Hutchinson[22] defined nine syndromes

Table VIII Incidence of complications

Hospital	Group	CHF and/or systolic blood pressure less than 90 without shock (%)	Shock (%)
A	Prior	14 0	4 2
	CCU	14 4	16 1
B	Prior	25 0	2 7
	CCU	39 6	13 8
C	Prior	46 9	4 8
	CCU	32 4	9 7
D	Prior	4 0	2 3
	CCU	6 2	4 6
E	Prior	7 3	3 9
	CCU	10 6	9 3

CHF = Congestive heart failure.

of congestive heart failure in acute myocardial infarction Lown and associates[24] found signs of congestive heart failure in 63 per cent of patients with acute myocardial infarction when careful attention was devoted to diagnosing this syndrome but they also noted that the mortality rate in patients who had congestive heart failure without pulmonary edema was 19 per cent while that for patients with pulmonary edema was 40 per cent.

In the study reported here the definition of each complication was left to the discretion of the senior cardiologist in the individual hospitals. Accordingly the admission severity classifications cannot be interpreted literally for all hospitals. An uncomplicated patient in one hospital may have been classified as complicated in another hospital In addition more intense examination in a CCU may have allowed the presence of a complication to be determined more readily (and thus more frequently) in the CCU versus a prior or regular care group Finally the retrospective analysis of prior patients compared with prospective study of CCU patients raises doubt as to comparability of data acquisition Although Table VIII indicates the CCU patients tended to be somewhat more severely ill the differences in each hospital are not sufficient to suggest that problems of definition of complications played a key role in the variable results found

The criteria for diagnosis of acute myocardial infarction may also affect hospital case fatality statistics. For example, a lower mortality rate appears to result from subendocardial infarctions compared to transmural infarctions.[28] In the series reported here subendocardial infarction accounted for 0 9 per cent of the CCU treated and 2 4 per cent of the prior-to-CCU treated group so this was not felt to be a factor

The time interval from onset of symptoms to admission to a CCU can have a significant effect on the hospital mortality rate.[29] Unfortunately data on onset to hospital admission for the prior groups were not always available for use in adjustment.

The criteria for patient inclusion in a study can also influence the final results. In this study patients who were admitted to the CCU more than six hours following hospital admission were not counted as CCU treated patients, even though these patients had a somewhat higher crude mortality rate than those patients who were admitted directly to the CCU This seemed to be a reasonable exclusion because of the known time-incidence of arrhythmias and death in acute myocardial infarction[9,26,27] Those patients who were not admitted directly to the CCU and did not receive intensive care during the critical first few hours after onset could not be properly included with those patients who did These patients were, however included in the combined after-CCU group to evaluate over-all hospital improvement.

True variation The design of this study attempted to exclude as many as possible of the above sources of variation in determining effectiveness within a given hospital no attempt was made to control for differences between any two hospitals. If all the assumptions concerning uniformity of definition within a given hospital are justified (and this is always open to question in any study collecting data from disparate sources) then the measurement of degree of effectiveness in a given hospital should be valid

Wide variation in CCU efficacy was found in the five hospitals studied Since

efficacy was based on comparison of CCU data to estimates derived from prior-to-CCU data, the variation could be due as much to differences in prior experience as to differences in CCU experience.

The data presented here then cannot be used to quantitate the over-all value of CCU's. This report only shows that, even in a study where an effort was made to avoid some of the difficulties felt to exist in other reports, a consistent pattern among individual hospitals could not be recognized.

The final answer as to how much the CCU has altered MI fatality will probably never be available The improvement should be reflected in general mortality statistics, but even this will probably not be definitive because of changes in diagnostic criteria.

Nevertheless, many physicians would agree that coronary care units when appropriately used can be beneficial in preventing deaths due to acute myocardial infarction. It has been this conviction, more than any firm statistical data, which has led to the rapid proliferation of coronary care units across the country It is perhaps most important now to concentrate efforts on the determination of the optimum way in which coronary care units can be utilized only when this is established will the maximum potential of CCU's be realized in all hospitals.

Summary

A study was undertaken to quantitate the effectiveness of coronary care units in reducing the hospital mortality rate from acute myocardial infarction. Five hospitals supplied data on patients treated before the CCU was opened (prior group) and on patients treated in a CCU The prior and CCU groups were classified according to age and admission severity and the observed CCU fatality rate was compared with an expected rate based on the prior experience. The effect on mortality ranged from −40 to + 1 per cent among the five hospitals. Additional variation could be shown by classifying data in different ways. The wide variation in effectiveness found in the literature may be due to differences of study design and statistical analysis and to inconsistent definitions and inclusion criteria. Although this study attempted to avoid these difficulties, the data presented still failed to show a consistent pattern of effectiveness within each hospital

The authors acknowledge the assistance of Mr Charles Bryant, National Center for Health Statistics, and Mr Morton Robins, Heart Disease and Stroke Control Program.

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Table VIII *Incidence of complications*

Hospital	*Group*	*CHF and/or systolic blood pressure less than 90 without shock* (%)	*Shock* (%)
A	Prior	14 0	4 2
	CCU	14 4	16 1
B	Prior	25 0	2 7
	CCU	39 6	13 8
C	Prior	46 9	4 8
	CCU	32 4	9 7
D	Prior	4 0	2 3
	CCU	6 2	4 6
E	Prior	7 3	3 9
	CCU	10 6	9 3

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Clinical evaluation of glucagon by continuous infusion in the treatment of low cardiac output states

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Study of the cardiovascular effects of glucagon in man have shown a positive inotropic and chronotropic effect resulting in an increase in cardiac output.[1-4] These effects occur one to 3 minutes after the intravenous injection of 3 to 5 mg. of glucagon and are dissipated in 30 minutes. These effects are similar to those of isoproterenol; however, glucagon has a limited chronotropic effect in man and has not caused arrhythmias even in the presence of digitalis. In contrast, a recent study of patients with chronic valvular heart disease concluded that these cardiac effects were variable, not dose-related, and of small magnitude when present. In addition to these cardiac effects, glucagon has been shown to increase renal excretion of water and electrolytes. Since previous studies are limited to the observation of the effects of a single bolus injection given to patients who were not in stress situations, it seemed appropriate to study the feasibility and efficacy of a continuous infusion of glucagon over a period of days in the treatment of conditions with low cardiac output or cardiogenic shock.

Methods

Lyophilized glucagon (Eli Lilly & Co.) was mixed with diluent and a small volume of 5 per cent glucose and water and placed in an in-line burette with an administration set adapter* to carefully control fluid volume and glucagon dosage. Since solutions of glucagon deteriorate at room temperature, these solutions were prepared fresh every hour. When potassium supplement was required, 20 mEq. of KCl was given orally or added to the intravenous fluids. Standard clinical techniques were used to record blood pressure and fluid balance. Blood glucose, serum Na^+, K^+, Cl^-, HCO_3^-, Ca^{++}, creatinine, and blood urea nitrogen were determined with standard techniques in the clinical pathology laboratories.

Table I lists the basic cardiac diagnosis and the clinical state of each patient at the time glucagon infusion was started as well as their response to therapy. Sixteen patients received 18 glucagon infusions at an average rate of 4.0 mg. per hour (1 to 16 mg. per hour) for an average treatment period of 4.9 days (0.1 to 12 days). All

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*Baxter Laboratories, Flexitrol Burette FA7M and set adapter R 4RM30.

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Appendix

The calculation of the statistical significance of the difference between expected fatality rates (adjusted for age and severity) and observed fatality rates was developed from the work of Chiang [28] Basically it involves a simple t test for the form

$$R = \frac{e - o}{s} \quad (1)$$

where e = expected rate (adjusted for age and severity) o = observed rate s = an estimate of the standard deviation of the difference between observed and expected fatality rates.

The estimate S is calculated by the equation

$$S = \sqrt{F + G} \quad (2)$$

where

$$F = \frac{1}{N^2}\left[\frac{n^2 (p q_1)}{n_{p_1}} + \frac{n_2^2 (p_2 q_2)}{n_{p_2}} + \frac{n^2 (p_3 q)}{n_p} + \frac{n^2 (p q)}{n_p}\right] \quad (3)$$

and

$$G = \frac{PQ}{N} \quad (4)$$

n = CCU cases in strata i Each age-severity subgroup becomes one of the four strata p = the proportion surviving in the prior strata q = the proportion dying in the prior strata n_{pi} = the number of cases in the prior strata P = the observed proportion surviving in the CCU treated group Q = the observed proportion dying in the CCU treated group N = the number of cases in the CCU treated group

If the value of R (from (1)) lies between 1 64 and 2 32 the difference is significant at the $p \lessgtr 0.05$ confidence level. If R is 2 33 or greater $p \leq 0.01$

patients were receiving digitalis. Only 2 of the 16 patients received diuretic agents during the first 24 hours of glucagon infusion. Cases 4 and 5 were on maintenance diuretics before and during the glucagon infusion and the dosage was not changed. Nine patients received diuretics later in the course of glucagon therapy to effect further diuresis during glucagon support of cardiac function.

Results

Blood pressure (*Fig. 1*). Five patients had no obtainable blood pressure at the time glucagon was started and 9 additional patients had systolic pressures of 90 mm. Hg or lower. Twelve of these 14 patients responded to glucagon with an increase in blood pressure. Two patients (Nos. 6 and 12) were in irreversible shock, unresponsive to vasopressors, for 14 and 12 hours, respectively before glucagon was started and died 6 and 2½ hours, respectively, after starting glucagon with no change in any parameter. One patient had severe hypotension reversed with isoproterenol infusion but because of tachycardia (140 per minute) and oliguria she was switched to glucagon with maintenance of blood pressure, an increase in urine output, and a decrease in heart rate. Two patients with normal blood pressures received glucagon therapy and there was no change in blood pressure or evidence of clinical improvement in their signs and symptoms of congestive heart failure.

The mean increase in systolic blood pressure was 34 mm. Hg ($p < 0.01$) and the mean increase in diastolic pressure was 28 mm. Hg ($p < 0.01$). The increase in blood pressure was seen within 15 minutes in 4 patients and as late as 90 minutes in one patient.

Urine output (*Fig. 2*). All patients who improved clinically had an increase in urine output. The mean urine output for the 8 hours before glucagon was 149 c.c. and for the first 8 hours on glucagon was 430 c.c., an average increase of 282 c.c. ($p < 0.01$). This 16 hour period was selected since no diuretic or other therapy was given or changed during this period which could have influenced this response to glucagon.

Heart rate and rhythm (*Fig. 2*). Six patients had atrial fibrillation as their basic rhythm, 9 had sinus tachycardia, and one had normal sinus rhythm (80 per minute). The mean ventricular rate before glucagon was 107 per minute. One patient had an increase in the ventricular rate from 70 to

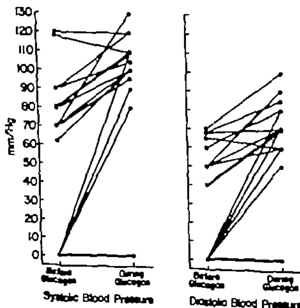


Fig. 1. Glucagon produced significant ($p < 0.01$) increase in systolic and diastolic blood pressure.

Table I Diagnosis clinical state and clinical response to glucagon therapy

Patient	Age	Diagnosis	Clinical state treated	Glucagon (mg/hr)	Days of glucagon	BP	Urine output	Heart rate	Clinical effect	Side effects
1	43	Rheumatic H D pulmonary emboli	Low cardiac output syndrome	2 0	12	↑	↑	↓	Improved	None
2a	60	Rheumatic H.D (MS, MI AS, and AI)	Chronic congestive heart failure	2 0	3	None	Slight ↑	↑	None	Nausea Hypoglycemia
2b	60	Rheumatic H.D 1 day after aortic and mitral replacement	Low cardiac output syndrome	4 0	7 2	↑	↑	No change	Improved	None
3	65	Rheumatic H.D (MS MI AS, and AI)	Chronic congestive heart failure	2 0	4 6	None	None	No change	None	Nausea
4	80	Arteriosclerotic H.D old myocardial infarct	Low cardiac output syndrome Pulmonary edema	3 9	2 6	↑	↑	No change	Improved	None
5	40	Starr Edwards aortic valve with SBE	Progressive congestive heart failure	10 0	8 2	None		↓	None	Nausea
6	58	Arteriosclerotic H.D acute myocardial infarct	Cardiogenic shock	4 0	0 25 (6 hr)	None	↓	No change	None	Nausea
7	44	Cardiomyopathy	Cardiogenic shock pulmonary edema	3 0	5 3	↑	↑	↓	Improved	None
8a	49	Cardiomyopathy	Cardiogenic shock	4 0	3 4	↑	↑	No change	Improved	Nausea
8b	49	Cardiomyopathy	Cardiogenic shock	4 0	1 4	↑	↑	↓	Improved	None
9	50	Cardiomyopathy	Cardiogenic shock pulmonary edema	4 0	4 6	↑	↑	↓	Improved	Nausea
10	57	Arteriosclerotic H.D acute myocardial infarct	Cardiogenic shock	4 0	3 4	↑	↑	↓	Improved	None
11	44	Arteriosclerotic H.D post-op. resection ventricular aneurysm	Low cardiac output syndrome	3 0	7 4	↑	↑	↓	Improved	None
12	63	Rheumatic H.D M.S. and T I	Cardiogenic shock after cardiac arrest	3 0	0 1 (2½ hr)	None	None	No change	None	None
13	53	Cardiomyopathy	Low cardiac output syndrome	3 6	6 5	↑	↑	↓	Improved	None
14	45	Rheumatic H D post-op. mitral valve replacement	Low cardiac output syndrome pulmonary edema	4 0	2 4	↑	↑	↓	Improved	None
15	53	Rheumatic H.D double valve replacement	Low cardiac output syndrome 8 hr post-op.	4 0	0 5 (12 hr)	↑	No change	↓	Improved initially then failed	None
16	35	Rheumatic H D mitral valve replacement	Low cardiac output post-op.	4 9	5 5	↑	↑	↓	Improved	None

Abbreviations H.D. = heart disease MS = mitral stenosis MI = mitral insufficiency AS = aortic stenosis AI = aortic insufficiency TI = tricuspid insufficiency SBE = subacute bacterial endocarditis.

80 per minute 3 patients were unchanged and all the other patients had a decrease in ventricular rate. The mean ventricular rate during glucagon therapy was 93 per minute, a decrease of 14 per minute ($p < 0.01$)

Five patients had paroxysmal arrhythmias during the 24 hours before glucagon was started. One patient had paroxysmal atrial tachycardia (PAT) with block due to digitalis toxicity one had paroxysms of atrial fibrillation and 3 had paroxysms of ventricular tachycardia. These patients had no paroxysmal arrhythmias during glucagon therapy

Serum electrolytes (*Fig 3*) In 4 patients glucagon infusion was instituted without potassium supplements. The mean serum potassium before glucagon was 4.5 mEq per liter and within 6 hours the mean potassium was 3.2 mEq per liter All of the other patients had 20 mEq of KCl along with the initial infusion of glucagon and there was no significant change in serum potassium 4.3 mEq per liter before glucagon and 4.2 mEq per liter after glucagon was started. Three patients developed hyperkalemia of 7 7 6.6 and 8 0 mEq per liter on the third, seventh and fifth days of glucagon infusions with KCl supplements which required discontinuing potassium and treatment with exchange resins. Two of these patients had failed to improve with glucagon and had deteriorating renal function with rising serum creatinines to 3.5 and 4 9 mg per cent, respectively The third patient was receiving 120 mEq of KCl supplements daily but had normal renal function studies and good urine output, and the reason for the hyperkalemia was not clear There was no significant change in other serum electrolytes.

Blood glucose Fifteen patients had no known abnormality of glucose tolerance and one patient had diabetes mellitus. The mean ± one standard deviation of all blood sugar determinations made in non diabetic patients while receiving glucagon was 151 ± 32 mg per cent. None of these patients required therapy for hyperglycemia. Patient 10 was a known diabetic controlled with oral hypoglycemic agents before her acute myocardial infarction On admission to the hospital her blood sugar was 384 mg per cent and insulin therapy was given. On the fourth hospital day the patient developed cardiogenic shock and glucagon therapy was started and insulin continued Myocardial infarction and glucagon would both be expected to increase the insulin requirement, and it was not possible to determine the specific effect of these two factors. No major change in insulin dosage was required.

Side effects The major side effect was nausea in 6 of the 16 patients. Nausea necessitated stopping the drug in one patient, at his request but was reasonably well tolerated in the other 5 Nausea appears to be dose-related but a specific dose level could not be determined due to individual patient variations.

The first patient to receive a continuous infusion of glucagon had a hypoglycemic reaction. The glucagon had been prepared to run over a 24 hour period. Twenty hours after this solution was started the patient developed atrial flutter with variable A V block and a ventricular rate of 140 to 160 beats per minute. The patient became dyspneic, diaphoretic, and had no obtainable blood pressure. A blood sample was collected and she was treated with 50 c.c. of a 50 per cent glucose solution a 2 mg bolus of glucagon and a fresh solution of glucagon was started. She also received 0 4 mg of lanatoside-C and 3 mg of morphine sulfate intravenously Laboratory data from the blood sample revealed a blood glucose of 40 mg per cent, serum sodium of 138 mEq per liter potassium of 6.3 mEq per liter and blood urea nitrogen of 60 mg per cent. One hour later she was comfortable with a ventricular rate of 90 per minute and a blood pressure of 94/70 mm. Hg Two days later the patient underwent successful replacement of her mitral and aortic valves, though she did require glucagon therapy in the postoperative period. This observation suggested that glucagon deteriorates in solution at room temperature. When glucagon infusions following this episode were freshly prepared every 4 hours, no further hypoglycemia was seen. When glucagon was discontinued a 5 per cent glucose-in water infusion was continued for 3 to 4 hours to prevent reactive hypoglycemia.

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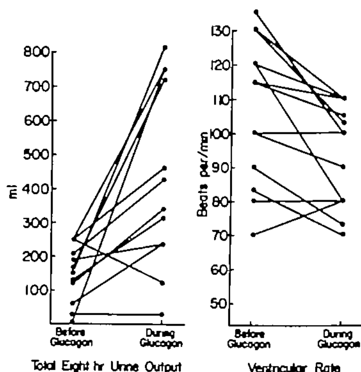


Fig 2 Glucagon produced a significant increase in urine output ($p < 0.01$) and a decrease in ventricular rate ($p < 0.01$) in patients with cardiac decompensation.

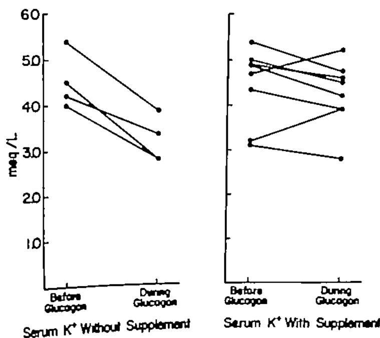


Fig 3 Glucagon produced a decrease in serum potassium which can be prevented by giving KCl supplements with the initial infusion.

highly efficacious in selected patients with severe cardiovascular disease states and is the treatment of choice in cardiac decompensation secondary to beta-blocking agents.

Addendum

Since this paper was written, Brogan, Kozonis, and Overy (Lancet 1:482 1969) in consultation with the authors, used the method for continuous glucagon infusion with a successful result in 4 patients.

The authors are grateful to Drs. Thomas A. Preston and Richard D Judge for their contribution of case material, to Drs. Herbert E. Sloan and Donald R. Kahn for their cooperation in the study of their patients, and to Dr F G. Henderson of Eli Lilly & Co., Indianapolis, Ind., who kindly supplied the glucagon used in this study

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Patient No 5 received glucagon at the rate of 16 mg per hour for 3 days and no toxic effects were seen in this patient nor in any other patients. There was no clinical evidence of tachyphylaxis.

Discussion

Glucagon is a polypeptide produced by the alpha cells of the pancreas and has been used clinically to treat hypoglycemia [6] evaluate hepatic glycogen stores [7] and as a provocative test for pheochromocytoma [8]

Lucchesi[9] and Glick and associates[10] have demonstrated that in the experimental animal beta receptor blockade with propranolol does not abolish the positive inotropic effect of glucagon This was demonstrated in our first patient who was admitted to University Hospital with a low cardiac output syndrome PAT with block due to digitalis intoxication and a blood pressure of 85/60 mm Hg Digitalis was stopped and since it was felt that the low cardiac output was secondary to the rapid rate 30 mg of propranolol were given orally with conversion of the rhythm to normal The oliguria and hypotension continued however and after the patient had received a total of 90 mg of propranolol over a 24 hour period glucagon was started Within 15 minutes after starting glucagon the blood pressure rose from 60/30 to 96/65 mm Hg and over the next 8 hours urine output increased Propranolol was then discontinued and no further arrhythmias were observed Glucagon appears to be the drug of choice in the treatment of excessive cardiac depression due to beta blocking agents.

Glucagon is known to increase the release of glucose from the liver and insulin from the pancreas. This results in an increase in peripheral glucose utilization and a transfer of extracellular potassium to the intracellular compartment with a resultant decrease in serum potassium This effect was clearly demonstrated in the 4 patients who received glucagon without initial potassium supplements. This is of major concern in patients of the type studied here, all of whom were on digitalis and subject to the potential risk of arrhythmias should significant hypokalemia develop. As demonstrated this hazard can be handled by starting potassium supplements with the glucagon however frequent serum potassium determinations are essential in following these patients since most (11 of 16) in this series have impaired renal function with elevated serum creatinines.

Glucagon has a positive chronotropic effect[11] though this is not as marked as that seen with isoproterenol This effect was not seen in this series of patients since most of them had severe cardiac decompensation and resultant tachycardias. When cardiac function was improved apparently due to the inotropic effect of glucagon infusion, the heart rate decreased This may be due to a decrease in sympathetic tone and decreased release of endogenous catecholamines in response to an enhancement of cardiac function The decrease in adrenergic drive might explain the apparent effect of glucagon in preventing arrhythmias in these patients including those who had paroxysmal arrhythmias in the 24 hour period before glucagon was started

In this series no improvement was seen in patients with long standing cardiogenic shock or in patients with chronic congestive heart failure who were maintaining a reasonable blood pressure Glucagon would appear to be most useful in the treatment of acute hypotension and shock as seen in patients with cardiomyopathies and acute myocardial infarction and in the low cardiac output state frequently seen following open heart surgery

Summary

A continuous infusion of glucagon in an average dose of 4 mg per hour over several days produced distinct improvement in the clinical state of 12 of 16 patients. Improvement was noted by an increase in blood pressure and urinary output and decrease in dyspnea pulmonary râles, diaphoresis, and peripheral edema when present. Serum potassium must be carefully monitored The rise in blood glucose has not been a clinical problem No cardiac arrhythmias were induced by glucagon and as cardiac function improved the heart rate usually decreased Nausea was the most frequent side effect, but no toxic effects or tachyphylaxis were observed. Long term therapy with glucagon infusion is both safe and

mounted at the tip of a fine plastic catheter which was introduced percutaneously from an arm vein into the superior vena cava or right atrium. Heart rate was counted from an electrocardiogram recorded for 15 seconds in each minute. The subject was first immersed supine in a hot bath (44° C.) for 10 to 20 minutes until the blood temperature approached 40° C Autonomic blockade was then produced by injecting 0.2 mg per kilogram of propranolol and 0.04 mg per kilogram of atropine intravenously over 2 minutes. Measurements of the IHR and blood temperature were begun 5 minutes later The bath was then changed to cold water (21 C.) causing blood temperature to fall by some 5° C. over the next 10 minutes. Finally hot water was reintroduced until the blood temperature rose again to its original level Paired measurements of blood temperature and the IHR were obtained from the fifth to the twentieth minutes after the injection of propranolol and atropine. To check the adequacy of autonomic blockade persisting after 20 minutes, a further injection was given containing half the original doses of both drugs this had no measurable effects on the heart rate

In each subject the changes in IHR and blood temperature were closely related with no apparent phase difference between the two. Over the temperature range studied the relationships appeared linear Table I gives the results of linear regression analysis of the data in each subject. These results were aligned by deriving in each subject the IHR at 37.5° C., and measuring increments in rate and temperature from this point Analysis of the pooled data then gave the relationship

$$\Delta \text{IHR} = -0.03 + 7\ 15\ (\Delta \text{ temperature}) \quad r = 0.94$$

Since the mean IHR at 37.5° C was 101.5 per minute the slope of the above relationship was close to 7 per cent per degree Centigrade rise in temperature which is equivalent to a Q_{10} value for the IHR of 1 7

In normal subjects at all ages, the 95 per cent limits of the IHR are approximately ±16 per minute from its mean value.[3] Because body temperature in different normal subjects at rest varies over only a small range temperature differences obviously cannot account for more than a very small part of the normal IHR distribution This was confirmed in 26 normal male subjects, 20 to 25 years of age by simultaneous measurements of the IHR and of deep muscle temperature. The latter was obtained from a thermistor mounted on a hypodermic needle, and inserted deeply into the deltoid muscle. Studies in 3 subjects showed that at rest, the temperature at this site was within 0 1 C of the mixed venous blood temperature. The mean IHR in the 26 subjects was 106 1 per minute (S.D 6.1) and the mean deep muscle temperature was 37.3° C (S D 0 5) Cor

Table I Analysis of the relationship between blood temperature and the intrinsic heart rate in 8 normal subjects

Subject No.	IHR at 37.5° C (beats/min.)	Temperature range studied (degrees C)	Linear correlation coefficient ( )	Slope (Δ IHR/degree C)
1	111	39 9–35 7	0 99	9 4
2	112	39 5–36 0	0 96	7 9
3	106	39 7 36 2	0 97	7 6
4	92	39 6–35 4	0 97	5 8
5	101	39 7–35 9	0 98	7 0
6	97	39 4–35 8	0 91	3 8
7	93	38 2 35 5	0 92	9 4
8	100	39 2 35 0	0 98	6 5
Pooled data	101 5 (S.D. 8)	39 9–35 0	0 94	7 15 (S.E. 0 19)

Experimental and laboratory reports

The effects of exercise and changes in body temperature on the intrinsic heart rate in man

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Previous studies of cardiac function after autonomic blockade by propranolol and atropine have revealed a relationship between the intrinsic rate of the heart and the contractile function of the myocardium both in healthy and diseased hearts in man[1-3] and during the production of experimental heart failure in animals.[4,5] The intrinsic heart rate (IHR) could be measured simply and safely in man and after preliminary studies[1] we suggested that this measurement might be valuable for the assessment of myocardial function in clinical practice To evaluate this suggestion extensive studies of the IHR have been made in normal subjects and in cardiac patients. Some determinants of the IHR in health have already been reported [3] In this study we have examined the effects of body temperature and exercise on the IHR in normal subjects

Methods and results

All studies were made on volunteer normal male subjects the majority of whom were medical students, and the remainder members of the Hospital staff Our criteria for normality in these studies were rigid and have been given in detail in a previous report [6]

The intrinsic heart rate (IHR) was measured during inhibition of autonomic nervous activity in the heart by an intravenous injection of propranolol 0.2 mg per kilogram and atropine 0 04 mg per kilogram given over 2 to 3 minutes. The selection of these drugs their doses and duration of action the extent of blockade they produce and the optimal timing of the IHR measurement in relation to their injection have all been examined and discussed in previous studies.[1,4] Here, as in previous studies, measurement of the IHR by this method was completely without complication confirming its very high level of safety in normal subjects.[1]

Estimates of significance were made by Student s t test, using paired comparisons whenever possible Changes in variance were tested by Fisher s F test.

I Body temperature changes The effect of changing body temperature on the IHR was studied in 8 normal males aged 20 to 23 years.

METHODS Central body temperature was measured continuously from a thermistor

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Table II. Mean measurements of oxygen consumption and cardiac performance, at rest and during light supine exercise before and after autonomic blockade in 6 normal subjects (mean body surface area, 1.75 M²)

	Oxygen consumption (ml./min./M²)	*Cardiac output (L./min./M²)*	*Heart rate (beats/min.)*	*Stroke volume (ml./M²)*	*Mean arterial pressure (mm. Hg)*
Control					
Rest	179 (28)*	3.7 (0.4)	73 (2)	51 (7)	102 (6)
Exercise	392 (26)	6.3 (0.9)	121 (7)	52 (6)	109 (7)
After autonomic blockade					
Rest	181 (14)	3.8 (0.6)	101 (4)	37 (2)	104 (3)
Exercise	389 (44)	6.3 (1.2)	113 (5)	56 (8)	106 (4)
Paired comparison of measurements during exercise	NS†	NS	$p < 0.02$	$p < 0.05$	NS

*Numbers in parentheses are the standard errors of the mean.
†Not significant.

changes in body temperature in the exercise-induced changes in heart rate was also studied.

METHODS. Each subject was studied at an environmental temperature of 70° C during a 5 minute control period of exercise, and 20 minutes later during the same exercise after autonomic blockade. Exercise was done upright on a Collins electronically braked bicycle ergometer at pedalling speeds of 80 to 100 per minute. The load which was independent of pedalling speed was set at 125 watts (760 kpm per minute) in the younger group and at 100 watts (610 kpm per minute) in the older. These work levels, chosen after a number of preliminary studies, were strenuous but not exhausting during the control exercise period but approached an exhausting level after propranolol and atropine. After a brief warm-up period and recovery the control exercise was performed at a steady rate for 5 minutes. Fifteen minutes was allowed for recovery. Propranolol and atropine were then injected intravenously and the second exercise period was begun 5 to 7 minutes later. One 23-year-old subject was able to complete only 3 minutes of the second exercise and his results were omitted from the analysis.

Heart rate was recorded throughout by a tachometer from a bipolar chest lead of younger subjects, deep body temperature was also measured by a thermistor probe passed into the esophagus to lie adjacent to the heart, below the tracheal bifurcation. In two preliminary studies, temperature at this site was within 0.2° C of right atrial temperature both at rest and during exercise, provided the probe was positioned below the tracheal bifurcation.

The results in the six 23-year-old subjects are shown in Fig. 1. Heart rate appeared to reach a plateau level during both exercise periods. In individual subjects this was more consistent after blockade than before. The mean rise in heart rate after one minute of exercise was reduced from 60 per minute in the control period to 13 per minute after blockade ($p < 0.001$). The maximum rise in heart rate during the exercise was reduced from a mean of 90 per minute in the control period to 25 per minute after blockade ($p < 0.001$). Body temperature changes were relatively small during both exercise periods. The maximum rise in the control study averaged 0.7° C., and after blockade 0.5° C.; these were not significantly different ($p > 0.3$). In each case the highest temperature was reached 1 to 2 minutes after exercise, by which time the heart rate had already fallen significantly from its highest level (Fig. 1).

The rapidity of the return of the IHR toward its resting value after exercise was of some interest. Two minutes after stop-

rection of the IHR in each subject to a temperature of 37.5° C using the relationship established above gave a mean value of 107.1 per minute (S.D. 5.5). This small resulting reduction in the variance of the IHR was not statistically significant ($F = 1.23$, $p > 0.05$).

II. Light exercise. It was found in our initial studies of the IHR that short periods of light exercise during cardiac catheterization caused no change in the measurement.[2] Prolonged light exercise, however, caused a gradual rise. This study was made to compare the cardiac responses to light supine exercise before and after autonomic blockade in 6 normal active but untrained subjects aged 18 to 36 years (mean 26) at environmental temperatures between 68 and 72° F.

METHODS. No premedication was given. Under local anesthesia a brachial artery was cannulated and a fine plastic catheter introduced percutaneously from an arm vein into the right atrium. Oxygen consumption was measured throughout using a low resistance closed-circuit spirometer system (Godart Pulmotest). Heart rate was measured from an electrocardiogram. Arterial pressure was measured from the brachial artery using a Statham strain gauge transducer. Cardiac output was measured by the dye dilution method injecting indocyanine green into the right atrium and recording its concentration in blood drawn from the brachial artery through a Gilford densitometer; this was calibrated by a pooled sample technique from the first dilution curve obtained in each subject; further details of these techniques have been given elsewhere.[3]

Exercise was carried out supine by pedalling a Collins electronically braked bicycle ergometer. The load was varied in different subjects between 40 and 60 watts (250 and 350 kpm per minute) so that the exercise could satisfactorily be reproduced over two consecutive 6 minute periods, and so that resting oxygen consumption was approximately doubled during the exercise. After a rehearsal of the exercise for 5 minutes a recovery period of 10 minutes was allowed. Control hemodynamic measurements were then made at rest. Exercise was then begun and further measurements recorded during the sixth minute. After another 10 minute rest period, propranolol and atropine were given together into the right atrium and 5 minutes later the hemodynamic measurements at rest and exercise were repeated in the same sequence.

The mean values of each measurement in the 6 studies are given in Table II. Comparison of the two sets of data at rest, describing the effects of autonomic blockade at rest, showed changes similar to those in a previous more detailed study[4]: there was no change in cardiac output, a marked rise in heart rate, and a fall in stroke volume. During the two exercise periods, at equal levels of oxygen consumption, the cardiac output was again the same before and after blockade; there was, however, a slightly lower heart rate and higher stroke volume after blockade (Table II). The manner in which cardiac output increased from rest to exercise differed after blockade in that there was less increase in rate (mean rise 48 per minute in control and 12 per minute after blockade, $p < 0.001$) and a greater increase in stroke volume (mean rise 1 ml. per square meter in control and 19 ml. per square meter after blockade, $p < 0.001$).

Autonomic blockade therefore limited but did not prevent an increase in heart rate on light exercise. The mean rise in the IHR of 12 per minute was highly consistent ($p < 0.001$). In 4 of the 6 subjects, a further intravenous injection of propranolol 0.2 mg. per kilogram and atropine 0.04 mg. per kilogram was given after the second set of measurements in exercise and the exercise continued for a further 3 minutes. This did not affect the level of heart rate; the maximum changes ranged from −3 to +2 per minute, averaging zero. Little or none of the IHR increase in exercise could therefore be attributed to incompleteness of the autonomic blockade.

III. Near maximal exercise. The effects of more severe exercise on heart rate before and after autonomic blockade were assessed according to age in 6 healthy active untrained students aged 23 years, and in 6 healthy moderately active men aged 45 to 55 years. In the younger group, the role of

triangles show the mean maximum heart rates during the control exercise period the squares show the mean maximum heart rates during exercise after autonomic blockade. These results are superimposed on the known relationships to age in normal subjects of the IHR at rest (lower dotted line) and of the maximal heart rate in exhausting exercise (upper dashed line) the close similarity between the rates of decline with age in these two measurements has been *noted and discussed previously*.[1] *In each* condition the mean heart rate in the younger subjects was faster than in the older subjects at rest the difference in IHR was 15 per minute ($p < 0.005$) during the control exercise the difference was 22 per minute ($p < 0.01$) and during exercise after blockade the difference was 13 per minute ($p < 0.01$) These three mean differences were not, however significantly different from each other ($p > 0.3$) In *other words, the* increases in rate above the intrinsic rate were equal in both younger and older subjects, both in the control exercise (mean values +77 per minute, S D 15 and +70 per minute, S D 8 respectively $p > 0.2$) and in exercise after blockade (mean values +27 per minute, S D 7 and +29 per *minute*, S D 2 $p > 0.6$)

Age, therefore, was associated with a fall of the *intrinsic* heart rate, but did not influence the *maximum* capacity of the heart to increase its rate in exercise above its intrinsic rate, either before or after autonomic blockade.

IV Exercise prior to measurement of the IHR. In previous studies of the serial reproducibility of the IHR in normal subjects, it was *noted that* moderate exertion prior to the measurement appeared to increase its variability To clarify this relationship serial studies were made here in two groups each of 15 normal *subjects*, one ranged in age from 20 to 25 years and the other from 40 to 50 years.

METHODS. Three measurements of the IHR were made in *each subject, at weekly* intervals. The first and second measurements were made between 9 and 11 A.M. without prior *exertion that* day at any level greater than *required* for slow walking The third was made under the same con-

Table III *Serial measurements of the IHR at weekly intervals in groups of 15 normal subjects ages* ?*0 to 25 and 40 to 50 years*

Measurement	Intrinsic heart rate (beats/min.)			
	Age 20 to 25 yr		Age 40 to 50 y	
	Mean	S.D	Mean	S.D
I	105 5	11 8	89 6	8 2
II	104 9	10 2	88 8	9 5
III†	105 1	5 6	96 3	5 6

*Measurement made without previous exertion on the day of study

†Measurement preceded by moderate exercise.

ditions except that it was preceded by a 15 minute period of strenuous exercise on a bicycle ergometer (*sufficient to increase the* heart rate above 120 per minute in each subject) the IHR was then measured as before, 15 minutes after completing the exercise. In 5 subjects from each group the order of the second and third measurements was reversed since, however this did not influence the results, these subjects *are not identified* further

The mean values of each of the three measurements and their distributions in each subject group are given in Table III To evaluate any effect of the exercise period on the subsequent IHR measurement, the differences between the first and second measurements were compared with the differences between the first and third. Three effects of the exercise were found (1) It significantly increased the random differences between successive *IHR* measurements. In the younger subjects the mean difference between paired IHR measurements was increased from 1.8 per minute (S.D 1.2) to 4 9 per minute (S D 1 4) and *in* the older subjects from 2 0 per minute (S.D 1 4) to 6 7 per minute (S D 3 9) In both groups together the estimated standard deviation of a single IHR measurement was ±1 6 per minute from the studies without prior exercise, and ±4.3 per minute when one study was preceded by exercise ($F = 7.0$ $p < 0.001$) (2) In the older but not in the younger subjects,

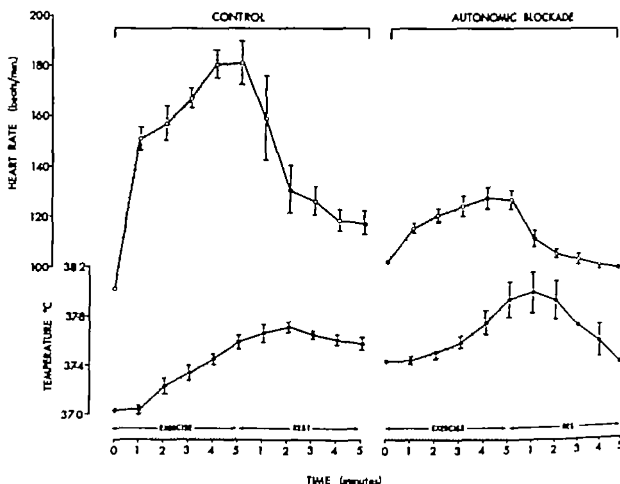


Fig 1 Simultaneous mean changes in heart rate and deep body temperature at one minute intervals during and after near maximal bicycle ergometer exercise in six 23-year-old normal subjects, *left* during control period of exercise, and *right* during the same exercise after autonomic blockade. Limits represent one standard error of the mean.

ping exercise the average IHR was only 3 per minute above its initial control value this difference was accounted for entirely by the increase of body temperature at that time which averaged 0 4 C Therefore whatever the mechanism for the major part of the increase in IHR its stimulus had totally disappeared within 2 minutes of stopping the exercise.

To examine the possibility that these changes in IHR during exercise arose from incompletely blocked sympathetic stimuli three additional studies were made in 20-year-old subjects. These were replicas of the exercise period after autonomic blockade except that during the fourth minute of exercise an additional 0.2 mg per kilogram of propranolol was injected through a polythene catheter inserted previously into the superior vena cava. The results were similar in each subject. The mean IHR after 3 minutes of exercise was 123 per minute the additional propranolol was given over the next minute at the end of which the mean IHR had risen to 128 per minute after a further minute at the end of exercise the mean IHR was 129 per minute No evidence was obtained to suggest that additional propranolol during exercise either lowered the IHR or limited any subsequent rise

In the older subjects, the patterns of heart rate change during exercise were closely similar From an initial value at rest which averaged 82 per minute heart rate rose during the control exercise to a maximum which averaged 160 per minute (S D 9) after blockade the IHR at rest averaged 90 per minute (S D 7) and increased in exercise to an average maximum of 119 per minute (S D 6) In Fig 2 the mean heart rates in the two groups are compared in relation to their ages the circles show the mean IHR at rest the

blockade. Under normal conditions in man, increases in heart rate in exercise are thought to be due to increased sympathetic stimuli, reduced vagal stimuli increased body temperature, and possibly other factors. In these studies, the dose of atropine given was sufficient to completely abolish vagal stimuli before exercise, and no increase in rate could therefore occur from their withdrawal during exercise. It is possible that some of the increase occurred from sympathetic stimuli which were incompletely blocked by propranolol. In this case however further propranolol during the exercise might have been expected to reduce the rate since its action is that of a competitive inhibitor [19] but in no case did this happen Moreover the increases in heart rate during strenuous exercise found by Donald and co-workers[20] in dogs after combined cardiac denervation and autonomic blockade by propranolol and atropine were very similar in magnitude to those found here in the IHR in man during near maximal exercise. It, therefore seems unlikely that the increases in IHR were

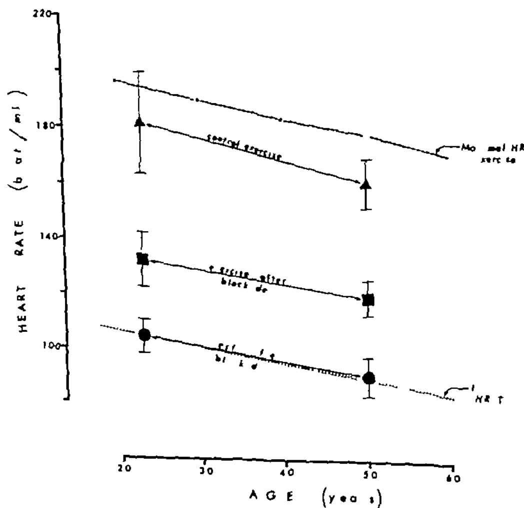


Fig 2. Mean values of the intrinsic heart rate at rest, and the maximum heart rates during exercise, before and after autonomic blockade in two groups of normal subjects, related to their age ● mean IHR at rest ▲ mean maximum heart rate during control exercise; ■ mean maximum heart rate during exercise after autonomic blockade; limits represent one standard deviation of the mean. Dashed line shows the maximal heart rate during exercise in normal subjects at different ages (mean values at each decade of age, compiled from the data of Robinson, Bruce and associates, Astrand, and Lester and co-workers[20]).

From Jose and Collison.

the measurement following exercise was in every case higher than the first measurement The average change in the older group was +6 7 per minute ($p < 0.001$) and in the younger group −0 4 per minute ($p > 0.8$) (3) Following exercise the range of the absolute IHR values in different individuals within each group was significantly reduced In younger subjects the variance was reduced almost threefold ($F = 2.7$ $p < 0.05$) and in older subjects twofold ($F = 2.1$ $0.1 > p > 0.05$)

No information was obtained concerning the possible mechanisms of these effects of prior exercise on the IHR measurement Of practical importance was the conclusion that for maximum serial reproducibility of the measurement in normal subjects, it was necessary to restrict exertion prior to the measurement. When this was done the standard deviation of a single measurement was only 1 6 per minute or 1 7 per cent which is not much larger than its possible error of counting

Discussion

Dependence of the IHR on body temperature was predictable Changes of 6 to 7 per minute per degree Centigrade in the spontaneous rate of the dog heart lung preparation were described many years ago [11] and changes of 6 per minute per degree Centigrade were found in an isolated perfused atrium from a 13 week human embryo [12] In dogs after autonomic blockade with propranolol and atropine we found changes in rate which averaged 6 4 per minute per degree Centigrade.[8] In all these cases as in the present study the relationship was apparently linear over the relatively narrow ranges of temperature studied

We have found under a number of other conditions that changes in the IHR were accompanied by proportional changes in the intrinsic contractility of the myocardium [1-4] No data was obtained in this study to show whether or not this was so during changes in body temperature in man. However in dogs under similar conditions of autonomic blockade we found no consistent changes in ventricular contractile force when body temperature was varied over the range from 35 to 40° C [8]

In man under normal conditions, fever is associated with variable increases of 20 to 35 per minute per degree Centigrade in the resting heart rate [8,13] Since from this study increases in the IHR contribute only 7 per minute to this figure, it is clear that the majority of the normal rate changes in fever must result from changes in the balance of neurohumoral stimuli to the heart.

Our studies in exercise were made primarily to observe and if possible to explain its effects on the IHR. The hemodynamic findings in light exercise also served to confirm the conclusions reached by Braunwald and associates[14] in a recent analysis of the normal cardiac response to exercise. These authors regard the normal response as an integration of the effects on the myocardium of simple tachycardia, sympathetic stimulation and operation of the Frank Starling mechanism when one or two of these is blocked the remaining mechanisms serve to increase cardiac output to a normal level for performance of light exercise although cardiac performance in strenuous exercise is significantly reduced [14] In this study after autonomic blockade cardiac output increased normally in light supine exercise there were, however greater increases in stroke volume and smaller increases in rate than in the control study suggesting that the Frank Starling mechanism was more important for the increase in output after sympathetic stimuli were blocked and rate increases were limited by propranolol and atropine. Similar conclusions to these have also been reached from studies of the exercise response in anesthetized dogs after cardiac denervation [15] in conscious dogs after chronic cardiac denervation [16] in normal human subjects after guanethidine and atropine [17] and in human patients with chronic lung disease after propranolol and atropine [18]

The mechanism of the increases in IHR found here in both exercise studies is of considerable interest These averaged 12 per minute in light exercise and 27 per minute in near maximal exercise each representing approximately one quarter of the heart rate increase found in the corresponding exercise before autonomic

practical importance for the interpretation of IHR changes observed serially in heart disease,[1] this effect of exercise was reinvestigated in the present study The results showed clearly that exercise before the measurement does have significant effects on the IHR. Although their mechanism was not studied and remains unknown, their practical importance is clear When significant exertion was avoided on the day of study the standard deviation of serial measurements was ±1 6 per minute Under such conditions, therefore serial changes in IHR greater than 3 per minute in any subject may be of clinical significance. Experience has shown that very much larger changes than this frequently occur in patients with known active heart disease.

Summary

The intrinsic heart rate (IHR) was measured after autonomic blockade by propranolol and atropine in normal human subjects during changes in central body temperature and at two levels of exercise

A direct linear relationship was found between the IHR and mixed venous blood temperature over the range from 35 to 40° C with a mean slope of 7 1 beats per minute per degree Centigrade.

The IHR increased during exercise both at mild and near maximal levels, in each case by approximately one quarter of the rate increase during the same exercise before autonomic blockade. Neither rises in body temperature nor incomplete blockade of sympathetic stimuli appeared to account for these changes. By analogy with the effects of early hypoxia on cardiac function in dogs after autonomic blockade, it is suggested that increases in the IHR in exercise may represent a direct response of the myocardium to mild hypoxia

Although in 50-year-old normal subjects the IHR was lower than in young adults, and the maximum heart rate in exercise was correspondingly lower the capacity to increase heart rate in exercise above its intrinsic level was equal at different ages.

Previous exercise increased the variability of serial measurements of the IHR in normal subjects. When exertion was avoided on the day of study paired measurements one week apart showed a standard deviation of 1 6 beats per minute, or 1 7 per cent.

We are grateful to the many volunteers who underwent these studies, and to Miss E. McLachlan, D.Sc., for her technical help. The studies of changes in body temperature were largely conducted by Drs. R Adler and N Olbourne during their tenure of Vacation Scholarships from the National Heart Foundation of Australia. Propranolol (Inderal) was freely provided by Messrs. I C.I. Pharmaceuticals, Ltd., Cheshire, England.

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simply a result of partial blockade of sympathetic stimuli. Increases in body temperature during exercise clearly played only an insignificant role in the IHR changes in these studies. No obvious explanation for the changes therefore exists.

Donald and Samueloff[21] obtained evidence that the analogous increase in heart rate on exercise in dogs after both surgical and pharmacological denervation of the heart is, in fact, myogenic in origin and not mediated by some blood borne substance.[21] Distension of the atria has long been known to cause changes in heart rate in intact animals,[22] and recent studies have shown that direct stretch of isolated sinoatrial pacemaker tissue increases its spontaneous rate.[23] It is possible that such a mechanism may operate in exercise after autonomic blockade in man, thereby increasing the IHR. However, in a previous study after propranolol and atropine in man, there was no change in the IHR during infusions of angiotensin which significantly increased the arterial, left ventricular end-diastolic, and right atrial pressures[7] nor could the rate changes provoked in cardiac-denervated dogs by intravenous infusions be directly related to right atrial pressure changes.[24]

Because the nature of the myocardial response to exercise is an adjustment from one level of tissue oxygen requirement to a higher level, there must be relative hypoxia of the myocardium, at least early in the response, and any such tendency would very likely be increased in hearts deprived of catecholamine activity. It is relevant, therefore, that in dogs after propranolol and atropine, the earliest functional cardiac responses to hypoxia, produced either by ventilation with 6 per cent oxygen or by infusion of sodium cyanide, were increases in both the IHR and myocardial contractility.[4] In those experiments, as in the present study, it was difficult to completely exclude the possibility that the functional changes had arisen from intense incompletely blocked sympathetic stimuli, but this appeared unlikely.[4] It is possible then that the increases in IHR in exercise in this study were analogous in origin to those found in dogs during early hypoxia, each representing the initial response of the myocardium to an imbalance between oxygen utilization and supply. If such an analogy is appropriate, the increased myocardial contractility which accompanied the increase in IHR in dogs[4] would imply that there was also a corresponding increase in contractility in exercise after autonomic blockade in man, although our measurements were not designed to provide any evidence of this. Together, such changes in the IHR and in myocardial contractility would comprise a significant fraction of the total capacity of the heart to increase its output in exercise after autonomic blockade.

From the data shown in Fig. 2, it appears clear that whatever the reason for the reduction in IHR at rest with age in normal subjects, this same factor is also responsible for the decrease with age in the maximal heart rate during exercise, both before and after autonomic blockade. There was no evidence that increasing age impaired the mechanisms which increased the heart rate in exercise above its intrinsic level. In all three conditions of heart rate illustrated in Fig. 2, the vagal inhibitory influence on heart rate was zero: it is known to be totally withdrawn in maximal exercise under normal conditions,[7,25] as in the control exercise measurements, and it was abolished by atropine in each of the others. Body temperature changes also were shown to be unimportant as factors in the cardiac acceleration in these studies. Two accelerator mechanisms, therefore, were concerned in producing the data shown: the known effect of increased sympathetic stimuli, and the possible mechanism already discussed for the exercise-induced changes remaining after autonomic blockade, which appeared to be nonadrenergic in nature. It was of some interest that neither of these mechanisms appeared to decline in capacity with age.

Previous studies of the serial reproducibility of the IHR in normal subjects over periods up to 10 months[5] showed that the measurement had a standard deviation of ±2.9 per minute, and similar values have been reported from other laboratories.[11,27] We noted in our study, however, that some of this variability was related to exertion prior to the measurement. Because of its

Assessment of the synergistic relationship between serum calcium and digitalis

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It has generally been accepted in clinical medicine that a synergism between calcium and digitalis on the excitability of the human heart existed. This clinical hypothesis is based, in part, on two case reports of digitalized patients dying shortly after receiving intravenous calcium, and is supported by a number of studies in animals. It has been shown in dogs that hypercalcemia produced by calcium chloride injection increases susceptibility to the action of ouabain.[3] This general fact has been confirmed by other studies, some of which assert a true synergistic relationship between calcium and digitalis,[4-6] and some, an additive relationship. Moreover, a digitalis tolerance test has been developed on the basis of the quantitative nature of this synergism. However, assessment of many of these experiments is difficult due to their uncontrolled nature.

Other investigators have come to contradictory conclusions regarding the relationship between calcium and digitalis. Parathormone injections were used to elevate serum calcium to 25 mg. per 100 ml. (12.5 mEq. per liter) in dogs, and no consistent increase in sensitivity to digitalis was noted. Only when large doses of calcium were given to produce characteristic electrocardiographic changes of hypercalcemia was the lethal dose of digitalis reduced. In another study[10] the toxic dose of acetylstrophanthidin was determined in dogs; at a later time various percentages of this toxic dose were administered and then the animals were challenged with large infusions of calcium. Even with serum calcium levels as high as 46 mg. per 100 ml. (23 mEq. per liter) an advanced degree of digitalization did not precipitate any digitalis arrhythmias. It was concluded from this study that in intact animals a calcium-digitalis synergism on cardiac excitation cannot be demonstrated.

In view of this continued controversy regarding the interrelationship of calcium and digitalis on the excitability of the heart, a study to examine quantitatively this relationship in intact dogs was designed. In this study calcium was infused at both high and low rates of infusion in order to

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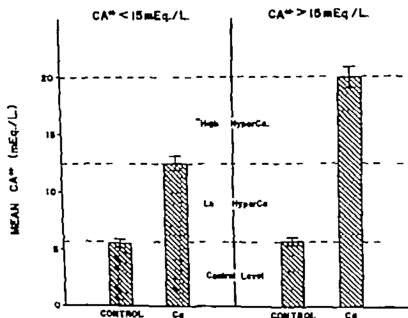


Fig. 1. The mean and standard errors of control and experimental calcium levels in groups of animals with "low" and "high" degrees of hypercalcemia.

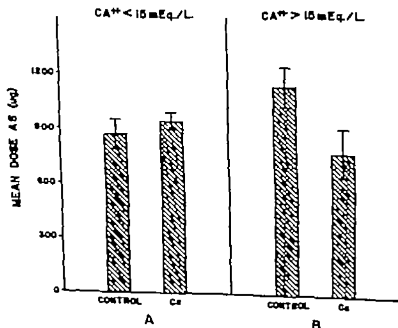


Fig. 2. The mean and standard errors of control and experimental doses of acetylstrophanthidin required to produce ventricular tachycardia (toxic dose) in "low" degree hypercalcemic animals (A) and in "high" degree hypercalcemic animals (B).

produce moderately elevated levels of serum calcium similar to that seen in clinical situations and to produce extremely high levels of serum calcium which might be seen with very large sudden injections of calcium. Each animal was studied for two days one with and one without calcium infusion each served as its own control in order to overcome the wide individual variations in amounts of acetylstrophanthidin necessary to produce toxicity.

Methods

Studies were performed in 21 dogs (11 to 30 Kg.) anesthetized with pentobarbital 30 mg. per kilogram. Small supplemental doses were given as necessary to maintain a moderate degree of anesthesia. Arterial pressure was measured with a P23Db Statham pressure transducer through a PE No. 260 cannula in the aorta via the femoral artery. Standard Lead II of the electrocardiogram and arterial pressure were recorded with a multichannel Beckman Model R direct writing oscillograph throughout the experiment.

Ventilation was maintained with a Harvard respirator through a cuffed endotracheal tube and was regulated to insure physiologic pH's and correct oxygenation. Blood samples from the femoral arterial cannula were analyzed for pO_2, pCO_2, and pH using a Model AME 1 Astrup ultramicro apparatus. The pH electrode was calibrated daily with standard solutions and duplicate pH determinations on blood samples were found to vary no more than ± 0.01 pH units. The pO_2 was determined with a modification of the Clark pO_2 electrode and duplicate determinations varied no more than ± 3 mm. Hg. Venous blood samples were taken from a PE No. 260 cannula in the femoral vein and serum calcium and potassium levels were determined with an atomic absorption spectrophotometer Perkin Elmer model 290.

An outline of the experimental protocol is as follows. Each experiment ran for two consecutive days, and each dog served as his own control in a randomized fashion. On both days two infusions were given (1) either of calcium chloride or saline and (2) of acetylstrophanthidin. On one day a solution of calcium chloride was infused at 1.0, 1.5, or 2.0 mEq. per minute, according to body weight for 30 minutes. An infusion of acetylstrophanthidin (123 µg per minute) followed as soon as possible after completion of the calcium infusion. Acetylstrophanthidin was infused until ventricular tachycardia occurred. The digitalis infusion was stopped immediately after the occurrence of ventricular tachycardia, which was defined in these experiments as the occurrence of 4 consecutive ectopic ventricular beats. Recovery from ventricular tachycardia was considered to have occurred when less than 6 ectopic beats per minute were recorded for 3 consecutive minutes. The arterial pressure and the electrocardiogram were continuously monitored from the beginning of the digitalis infusion to the occurrence of ventricular tachycardia (from which the dose of acetylstrophanthidin needed to produce toxicity was calculated) and to the time of recovery. A normal saline infusion in lieu of calcium was given on the control day under similar conditions immediately followed with acetylstrophanthidin 123 mg. per minute. The same circulatory variables were monitored in these experiments. The order of the control day (when only saline and digitalis were given) and the experimental day (calcium and digitalis) was randomized so that neither day was always the first in this 2 day study. It should be noted further that a 24 hour period was sufficient for elimination of digitalis since it has been shown in earlier studies by Kleiger and associates[11, 12] that the toxic dose of acetylstrophanthidin was not significantly altered when three hours were allowed to elapse between digitalis infusions.

Venous blood samples were taken on both days at certain points during the experiment: before any infusions of calcium or saline at 15, 20, 25, and 30 minutes after the beginning of the first infusion, at the time of ventricular tachycardia, and at the time of recovery from ventricular tachycardia. Arterial blood gas samples were taken at control time, at the end of the first infusion, at the time of onset of ventricular tachycardia, and at the time of recovery. All solutions were infused with a Harvard infusion pump through a PE No. 260 cannula in the jugular vein.

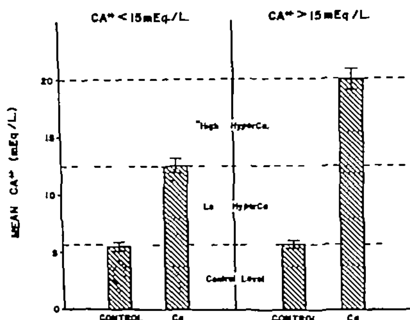


Fig. 1 The mean and standard errors of control and experimental calcium levels in groups of animals ith "low and "high degrees of hypercalcemia

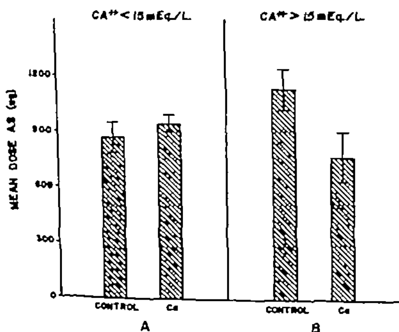


Fig. 2. The mean and standard errors of control and experimental doses of acetylstrophanthidin required to produce ventricular tachycardia (toxic dose) in "low degree hypercalcemic animals (A) and in "high degree hypercalcemic animals (B)

Results

Studies to determine toxic dose Significant difference in the dose of acetylstrophanthidin required to produce ventricular tachycardia in animals with normal as compared to animals with abnormally high levels of serum calcium was found to exist only when the serum calcium level exceeded a certain threshold value The experimental group of animals accordingly was divided into two groups one group of 9 dogs representing a low degree of hypercalcemia whose serum calcium levels after calcium infusion were less than 15 mEq per liter (30 mg per cent) and a second group of 12 dogs representing a high degree of hypercalcemia whose serum calcium levels exceeded 15 mEq per liter (Fig 1) The low group had a mean calcium level of 12 48 ± 0 61 mEq per liter (25 0 ± 1.2 mg per cent) while the high group had a mean level of 19 94 ± 0 91 mEq per liter (39.9 ± 1 8 mg per cent)

The average toxic dose of acetylstrophanthidin was not significantly affected when accompanied by a low degree of hypercalcemia (Fig 2 A) However when calcium levels were greater than 15 mEq. per liter the mean toxic dose of digitalis was found to be significantly smaller ($p < 0.05$) (68 per cent of the control toxic dose) than the control value (Fig 2 B) There was a significant difference between the amount of acetylstrophanthidin necessary to produce ventricular tachycardia in the control situation for the low and high calcium levels (Fig 2) which tends to emphasize the need for using each series of animals a

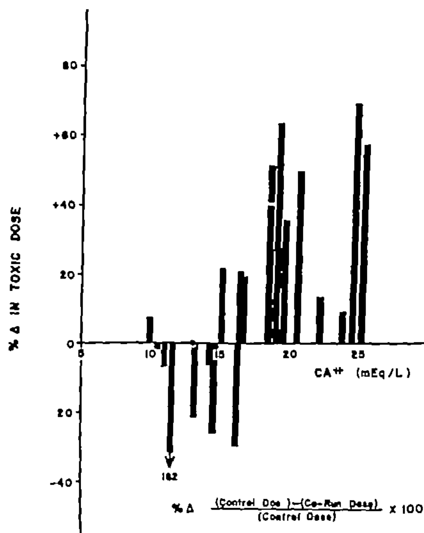


Fig 3 The percentage change in toxic dose of acetylstrophanthidin at various serum calcium (CA^{++}) levels in 21 individual experiments.

its own control. (The average weight of dogs in both groups was the same, and therefore did not affect the significance of the difference between the control toxic doses for the two groups of animals.) The significant difference between the control and experimental toxic doses for the "high" calcium group is also reflected in the large, positive percentage changes in the toxic dose of acetylstrophanthidin for individual dogs with calcium levels greater than 15 mEq. per liter (Fig 3)

Four additional dogs were given calcium chloride at a constant rate of 2.0 mEq per minute until death Serum calcium levels were determined at the point of death in order to establish the fatal calcium level in dogs (Table I) The mean fatal calcium level was found to be 30.25 ± 1 70 mEq per liter (60.5 ± 3 4 mg per cent) It should be noted that the mean calcium level for the "high" group of animals represents 66 per cent of the fatal calcium level Three more dogs were given the usual calcium infusions, which were not followed by digitalis in order to show that calcium at the levels obtained experimentally in our studies was not fatal and did not produce ventricular arrhythmias.

Studies to determine duration of toxicity The duration of ventricular arrhythmia produced by acetylstrophanthidin was not significantly different in animals with hypercalcemia when compared to animals with normal calcium levels (Table II) In the course of this study however 6 dogs died of ventricular fibrillation after the toxic end point had been reached Only one had normal serum calcium levels, while the other 5 had calcium levels in excess of 18 mEq per liter (36 mg per cent)

Serum potassium hemodynamic variables and blood gases Serum potassium increased significantly ($p < 0.05$) during acetylstrophanthidin infusion in both normal and hypercalcemic animals (Table III) However there was no difference between the increments seen in the control group and those in the experimental group (Table III)

Acetylstrophanthidin produced a marked significant ($p < 0.01$) slowing of the ventricular heart rate prior to the onset of ventricular tachycardia (Table III) Mean arterial blood pressure was increased by the infusion of acetylstrophanthidin in each group of animals studied (Fig 4) When the pressure trends of both groups were compared it was found that the mean pressures during calcium and digitalis infusion were significantly higher ($p < 0.05$) than the corresponding pressures in the control group (Fig 4)

The data in Table III also show that blood pH pO_2 and pCO_2 were maintained within normal physiologic range during the entire course of all of these experiments.

Electrocardiographic changes During the administration of acetylstrophanthidin the electrocardiographic sequence of events usually began with S-T–segment depression,

Table I *Fatal calcium levels*

Experiment N	*Ca level (mEq./L.) at death (VF)*
1	25 50
2	31 50
3	33 50
4	30 50
Average	30 25 ± 1 70

VF Ventricular fibrillation.

Table II *Duration of toxicity*

Dog No.	*Duration (min.)*	
	Control run	*Calcium run*
5	7 5	13 0
8	13 0	17 0
9	20 0	17 0
11	5 0	6 0
12	9 0	8 5
13	44 0	8 5
15	6 0	7 0
16	3 0	24 0
18	41 0	21 0
19	21 0	17 5
20	15 0	31 5
21	21 0	12 0
Average	17 1 ± 4 0	15 2 ± 2 2

Table III *Serum potassium heart rate and blood gases*

Parameter	No. dogs	Control run				Calcium run			
		Control	End Na+	VT	Rec.	Control	End Ca++	VT	Rec.
Serum potassium (mEq./L.)	11	4.31 ± 0.28	4.06 ± 0.26	4.84 ± 0.16	4.60 ± 0.23	4.35 ± 0.18	4.14 ± 0.20	4.89 ± 0.21	4.93 ± 0.17
Heart rate per minute	12	166 ± 8	166 ± 8	143 ± 7	178 ± 6	171 ± 6	167 ± 8	132 ± 10	182 ± 9
pH	11	7 43 ± 0.01	7.39 ± 0.01	7 42 ± 0.01	7 40 ± 0.02	7 40 ± 0.02	7.35 ± 0.01	7.34 ± 0.01	7.34 ± 0.01
pO_2	11	109 ± 3	110 ± 3	115 ± 4	110 ± 3	105 ± 3	105 ± 2	104 ± 4	105 ± 3
pCO_2	10	28 ± 1	32 ± 1	27 ± 1	26 ± 1	32 ± 1	32 ± 2	29 ± 2	28 ± 2

Abbreviations End Na+/Ca++ = Values at the end of sodium or calcium infusion VT = at the time of onset of ventricular tachycardia; Rec. = at the time of termination of ventricular tachycardia.

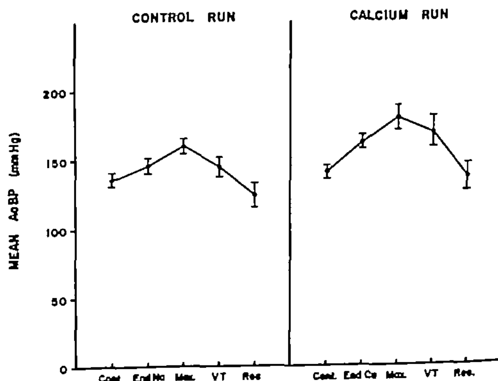


Fig 4 The mean and standard errors in aortic blood pressure at various times during control (without calcium) and experimental (with calcium) studies for 13 dogs. Abbreviations *AoBP* = Aortic blood pressure *End Na+/Ca++* = end of sodium or calcium infusion *Max* = maximum pressure during digitalis infusion *VT* = onset of ventricular tachycardia *Rec* = termination of ventricular tachycardia

accompanied by gradual sinus slowing and prolongation of the P R interval This was followed by occasional ventricular premature beats and then by the sudden onset of ectopic ventricular tachycardia with atrioventricular dissociation This sequence of events was not constant, since some dogs exhibited a different sequence e.g abrupt onset of ventricular tachycardia without occasional premature ventricular contractions. Nonetheless, the sequence exhibited by a given animal was usually constant for both control and experimental days.

Discussion

Although a number of clinical and laboratory studies have suggested a relationship between high levels of serum calcium

and enhanced sensitivity to the toxic arrhythmic effects of digitalis glycosides these studies have not clearly defined this relationship in a quantitative manner[1,7] The results of this study demonstrate a synergistic effect between calcium and digitalis, in that extremely high levels of serum calcium (greater than 15 mEq per liter or 30 mg per cent) do lead to the appearance of digitalis toxic arrhythmias with the administration of significantly smaller doses of acetylstrophanthidin than those required at lower or normal levels of serum calcium The moderately elevated low levels of serum calcium produced in our study by infusion of calcium chloride averaged 12 48 mEq per liter (25 mg per cent) and in these animals the amount of acetylstrophanthidin required to produce digitalis-toxic ventricular tachycardia was not significantly different from the control animals with normal serum calcium. The high levels for serum calcium averaged 19 94 mEq per liter (40 mg per cent) and resulted in the production of digitalis-induced ventricular tachycardia with infusion of significantly less acetylstrophanthidin It is interesting to note that the level of serum calcium required to enhance digitalis toxicity was approximately two thirds of that necessary to produce death by hypercalcemia in other animals studied.

These findings are in contrast to those of other investigators, [11] who reported that the toxic and lethal effects of calcium and digitalis are neither synergistic nor additive Lown and associates[1] have reported that digitalis toxic arrhythmias were precipitated by calcium (as high as 23 mEq per liter or 46 mg per cent) only when animals had received more than 95 per cent of the toxic dose of digitalis. In our study similar results were occasionally obtained for animals with calcium levels near 15 mEq per liter (30 mg per cent) and digitalis intoxication was consistently produced in dogs having an average serum calcium level of 19 94 mEq per liter with an average dose of acetylstrophanthidin representing only 63 per cent of the control toxic dose. This discrepancy may be accounted for partially by the fact that the other investigators[1,11] did not measure or control pO_2. Hypoxia is an important factor in the production of cardiac arrhythmias (wide variations in the toxic dose of acetylstrophanthidin in normal and hypoxic dogs have been observed[14] and did not occur in our studies) Moreover much of the difficulty in the interpretation of earlier studies results from a failure to control or measure oxygen or pH changes induced during long studies in which animals were under general anesthetics.[2,4,9] Finally the studies of Lown and associates[10] and of Smith and co-workers[11] are not directly comparable, since these investigators administered digitalis before the administration of calcium, not after hypercalcemia had been produced as in our study

Although the infusion of acetylstrophanthidin produced elevations of serum potassium hypercalcemia did not significantly alter this action of the acetylstrophanthidin The increase in arterial blood pressure produced by acetylstrophanthidin was greater in the hypercalcemic animals, however This would suggest a synergistic effect of calcium and digitalis as an enhancement of the inotropic action or greater arterial constriction or a combination of both The elevation of serum potassium and the increase in arterial pressure produced by acetylstrophanthidin have been described previously[14-1]

Although the duration of toxicity to acetylstrophanthidin was not altered by hypercalcemia, the rapid progression of 5 hypercalcemic animals to ventricular fibrillation after the toxic end point had been reached makes this point difficult to assess with certainty Perhaps this too could be considered evidence for the concept that high levels of serum calcium enhance digitalis toxicity since this has been observed infrequently in normal animals being administered acetylstrophanthidin in amounts necessary to produce ventricular tachycardia.

This study does not permit a precise definition of the mechanism for the enhancement of digitalis toxicity by elevated serum calcium. However several mechanisms may be postulated First, since the transport of calcium from the sarcoplasmic reticulum into the myocardial cell is altered by digitalis, it seems possible that large amounts of calcium would be available for

transport when serum calcium is elevated This appears reasonable since the inotropic effects of digitalis are enhanced by hypercalcemia[17] Thus the greater calcium transport associated with the administration of acetylstrophanthidin may result in enhancement of ventricular arrhythmias Second calcium may be important in the transport of digitalis into the myocardial cell or in its binding within or on the cell membrane. It is interesting to speculate that higher calcium levels result in higher intracellular or bound digitalis levels. Studies utilizing radioactive labelled digoxin are in progress to elucidate this possible mechanism Third both digitalis and high concentrations of calcium produce a change in the permeability of the cell membrane to potassium such that their administration is known to promote the outflow of potassium from the myocardial cell[18] Thus the lowered cellular potassium results in increased irritability of the myocardium and enhancement of digitalis toxicity

Finally while it is difficult to evaluate these experimental data in terms of clinical problems several salient points appear to be justified The levels of serum calcium found to be necessary experimentally to produce enhancement of digitalis toxicity are not encountered clinically even in the most extreme cases of disease related to calcium metabolism For example even in overt hyperparathyroidism sarcoidosis or vitamin D poisoning serum calcium levels seldom exceed 10 to 12 mEq per liter (20 to 24 mg per cent) Thus it seems unlikely that high serum calcium levels encountered in patients with various diseases are such that they lead to enhancement of digitalis toxicity Conceivably however exogenous administration of large amounts of calcium or bolus injection of calcium as is sometimes used in resuscitation attempts, could transiently produce serum calciums in excess of 15 mEq per liter It therefore seems appropriate to suggest that calcium be administered slowly or in small amounts in these situations to patients receiving digitalis glycosides.

Summary

The relationship of moderately high and of very high levels of serum calcium to the enhanced sensitivity to the toxic arrhythmic effects of digitalis glycosides was studied It was shown that with serum calcium levels greater than 15 mEq per liter (30 mg. per cent) digitalis toxic arrhythmias could be produced with significantly lower doses of acetylstrophanthidin (approximately two thirds the toxic dose) than those needed at lower and normal calcium levels. Under the combined conditions of hypercalcemia and digitalis increases in arterial blood pressure caused by digitalis were greater while digitalis-induced elevations of serum potassium and duration of toxicity to acetylstrophanthidin were not significantly different from control values.

Possible mechanisms for the potentiative effects of calcium and digitalis consist of the following (1) Large amounts of calcium available for transport in association with digitalis may precipitate ventricular arrhythmias (2) the possible importance of calcium in the transport and/or binding of digitalis in the myocardial cell (3) an efflux of intracellular potassium from the cell caused by both digitalis and high calcium levels.

Clinically speaking serum calcium levels as high as those produced in this study for the enhancement of digitalis toxicity are not encountered even in extreme pathologic conditions related to calcium metabolism. However it is suggested that calcium be given slowly or in small amounts to digitalized patients, in order to avoid transient calcium levels greater than 15 mEq per liter which may be produced by large or rapid intravenously administered doses of calcium

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whom were considered healthy on the basis of history and routine physical and laboratory examinations. They ranged from 21 to 61 years in age with a mean age of 41.3 years.

Three orthogonal leads, X, Y, and Z, were recorded simultaneously at a paper speed of 25 mm. per second and at a sensitivity of approximately 30 mm. per millivolt using the Frank lead system with subjects in the supine position and with the chest electrodes placed at the level of the fifth intercostal space. Recording was made on photographic paper by means of an Electronics for Medicine DR-8 recorder. The amplitude of each wave of the QRS-T complex was manually measured in each lead and was expressed in millivolts (mv). Amplitude ratios of the Q and S to the R wave were calculated in each lead, and the T/R was also determined except in Lead Z.

Recognition of infarction patients was evaluated on each item, first using the 95 per cent limits for the normal series. In Q and S amplitudes and their ratios to the R amplitude in Leads X and Y, the ninety-fifth percentile point for the normal series was adopted as the upper limit and the lower limit was set at zero, since zero was considered normal for these items. For the rest of the items the lower limit was set at the 2.5 percentile point, and the upper limit at the 97.5 percentile point.[4] In a later part of the present study a probability density function assumed for each of 3 lead Q/R ratios was utilized for respective normal limits for these items (Appendix 2).

Departure from normality was assessed on the frequency curve of each item for the normal series using Fisher's criteria[5] (Appendix 1). Chi-square tests were performed to evaluate goodness of fit to an exponential distribution on the frequency curve of the Q/R ratio in Leads X and Y for the normal series (Appendix 1). Logarithmic transformation of variates was employed to approximate to a normal distribution the frequency curve of the Q, R, and Q/R in Lead Z for the normal series (Appendix 1). A two-dimensional rejection ellipse[6,7] was determined for the log-normalized Q and R in Lead Z (Q, R) in the normal series on the assumption of a bivariate normal distribution for the normalized data.

Most of the computation was made with use of a digital computer, PDP 8, at the Laboratory of Physiological Hygiene, University of Minnesota.

Results

Table I shows the normal 95 per cent limits for each item analyzed in the present study and the recognition rate in the infarction patients.

The recognition rate of the Q amplitude

Table I. Recognition rates for wave-amplitude measurements in Frank orthogonal leads in 114 infarction patients

Parameter	Lead X		Lead Y		Lead Z	
	Normal limits	Recognition (%)	Normal limits	Recognition (%)	Normal limits	Recognition (%)
Q amplitude (mv.)	0 to 0.14	4.4	0 to 0.20	25.4	0.08 to 0.65	43.0 (43.0)
R amplitude (mv.)	0.48 to 1.56	28.9 (24.5)	0.20 to 1.63	26.3 (26.3)	0.27 to 1.22	16.6 (5.3)
S amplitude (mv.)	0 to 0.34	4.4	0 to 0.22	23.7	0	6.1
T amplitude (mv.)	0.07 to 0.46	35.2 (33.5)	0.06 to 0.44	43.8 (43.0)	−0.44 to −0.04	27.2 (5.3)
Q/R ratio	0 to 0.13	17.5	0 to 0.19	48.2	0.14 to 1.38	56.1 (53.5)
S/R ratio	0 to 0.48	12.3	0 to 0.54	28.9	0	6.1
T/R ratio	0.08 to 0.52	51.5 (48.2)	0.07 to 1.01	46.5 (35.1)	—	—

*The numbers under the heading of "Recognition" indicate percentages of infarction patients whose value for the corresponding item exceeded the normal limits. Those in parentheses represent percentages of patients whose value was below the lower normal limit. The normal limits for each item are the 95 per cent range for [illegible] healthy men, and the limit values on both ends are regarded as normal.

Recognition of myocardial infarction by means of Frank lead Q/R ratios

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The two principal methods of electrocardiographic data display currently in clinical use are the scalar and the vectorial representations. The scalar representation requires a less expensive recording system and provides for more easily and accurately obtained manual measurements than does the vectorial display These features of the scalar display are advantageous in both clinical and epidemiologic application

On the other hand the redundancy of information regarding wave form configuration in the conventional 12 lead electrocardiogram (ECG) has been well recognized and was quantitatively demonstrated by Simonson Cady and LaRiviere [1] Abildskov and colleagues[2] showed that most but not all of the information of known clinical significance in the 12 lead ECG appeared in recognizable form in the 3 Frank system leads. In comparative analysis of the 12 leads and the SVEC III leads of 261 patients with ECG abnormalities Pipberger and associates[3] demonstrated that all information of clinical significance in the conventional ECG could be retrieved from the 3 orthogonal leads except in 7 3 per cent of the patients and from resolved orthogonal leads except in one patient

The present study was undertaken to establish simple criteria for differentiation between patients with myocardial infarction and normal subjects on the basis of the wave amplitudes and the amplitude ratios of the QRS-T complexes in the 3 Frank system leads.

Material and methods

The material of the present study consisted of 114 male patients with myocardial infarction admitted to the Minneapolis Veterans Administration Hospital and 155 healthy men All patients had an unequivocal past or recent history of acute myocardial infarction [4] The presence of previous acute infarction was confirmed by reviewing series of conventional ECG s as well as serial examination of serum enzyme such as glutamic oxalacetic transaminase and creatine phosphokinase activity Their mean age was 57 8 years with a range of 35 to 77 years. Patients with a QRS duration of more than 0 12 sec were excluded from the present study The normal control subjects were hospital employees all of

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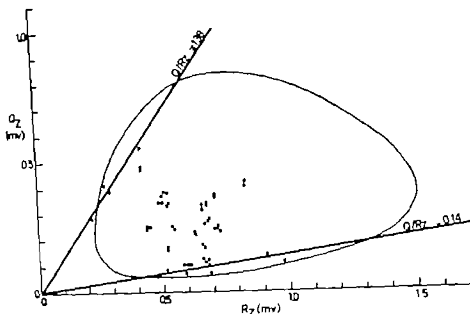


Fig 3 The combined distribution of the Q and R amplitudes in the Frank Lead Z for 155 healthy men. The two oblique lines represent the geometrical version of the upper and lower limits for the normal Q/R range. The closed curve indicates rejection ellipse calculated from the logarithmic-transformed R and Q_z for the normal series. Cases outside the ellipse will be regarded as abnormal at risk of 5 per cent in respect to R and Q_z. Note that the Q/R limits fit the upper left and the lower boundary of the ellipse.

item (approximately 55 per cent) and those in Lead Y also showed relatively high recognition rate (approximately 45 per cent) Nevertheless, the T abnormalities are not specific for myocardial infarction.

Thus the Q/R ratios were considered as the most important among the items analyzed in the present study This conclusion provided a basis for investigation of the combined distribution of the Q and R amplitudes. The scatter diagrams of Leads X and Y for the normal series were quite unique in pattern of distribution and showed a striking similarity (Figs. 1 and 2) As the R amplitude increased, the upper limit of normal Q amplitude increased apparently as a linear function of R, however the lower limit for normal Q amplitude appeared to remain fixed at zero. In these figures the oblique line through the zero point indicates the geometric version of the normal upper Q/R limit (the ninety-fifth percentile point of the normal series) and the abscissa corresponds to the lower limit of the ratio (the 0 percentile point) It is of interest to note how well these two lines fit the boundary of the combined distribution. In contrast, the line parallel to the abscissa, which indicates the upper Q limit does not effectively outline the combined distribution The scatter diagram for Lead Z is shown in Fig 3 where the closed curve indicates the linear-scale representation of the rejection ellipse calculated from the log-normalized data for Q and R amplitudes in the normal control The curve is expected to include 95 per cent of subjects in the population of healthy men in respect to these two amplitudes. Here again the oblique lines representative of the upper and lower normal Q/R limits (the 2.5 and 97.5 percentile points) seem to fit, respectively the left and the lower boundary of the rejection ellipse. This observation is

*The ellipse is explicitly expressed in the following formula. [illegible] $XY + 4$ [illegible] $= F_{0.95}$ [illegible], where $X = \log_e (R_z + 0$ [illegible]$) + 0.$[illegible] and $Y = \log_e (Q_z + 0$ [illegible]$)$ $+ 0.$[illegible] with both R_z and Q_z expressed in millivolts, and $F_{0.95}$ [illegible] is the ninety-fifth percentile point of F distribution with degrees of freedom = 2 and 15[illegible].

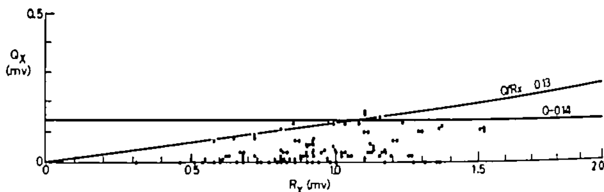


Fig 1 The combined distribution of the Q and R amplitudes in the Frank Lead X for 155 healthy men. The upper limits of the normal 95 per cent range for the Q/R and the Q amplitude are indicated by an oblique line and a line parallel to the abscissa respectively and the lower limits for both items are the abscissa itself Note that the Q/R limits better outline the combined distribution than the Q limits.

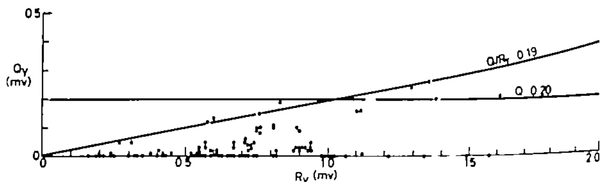


Fig 2 The combined distribution of the Q and R amplitudes in the Frank Lead Y for 155 healthy men. The upper limits of the normal 95 per cent range for the Q/R and the Q amplitude are represented by an oblique line and a line parallel to the abscissa, respectively and the lower limits are the abscissa itself Note that the Q/R limits better outline the combined distribution than the Q limits.

in Lead X (Q) was so low as to be comparable with the false abnormality in the normal series In contrast the Q in Lead Y (Q_y) discriminated one fourth of infarction patients. The Q generally tended to be smaller in amplitude in patients with infarction than in normal subjects and more than 40 per cent of patients were discriminated by this measurement On the other hand the Q/R ratio invariably showed a higher diagnostic performance than the Q amplitude in each lead A remarkable difference in recognition was observed between these items in Lead Y where the Q/R was nearly twice as discriminative as the Q amplitude (48 2 versus 25 4 per cent) The Q/R in Lead Z was found to be the most discriminative among all items analyzed in this study (56 1 per cent) while Q/R in Lead Y marked as the fourth most discriminative

The recognition rate for the R amplitude was low and less than 30 per cent in each lead Nevertheless it is diagnostically interesting to note that the mean R amplitude in Leads X and Y was significantly smaller in infarction patients than in the normal control subjects. Since this tendency was just opposite to that for the Q amplitude in these leads the diagnostic performance of the Q/R ratio was enhanced

The S and S/R in Lead Y tended to be greater in infarction patients than in normal subjects although showing a low recognition rate of approximately 25 per cent This indicates that the QRS tends to show superior deviation of the axis possibly due to peri infarction block in some cases

The T wave in infarction patients showed a significantly smaller mean amplitude in Leads X and Y and a significantly larger mean in Lead Z than in normal subjects. The T measurements in Lead X were found to be the second most discriminative

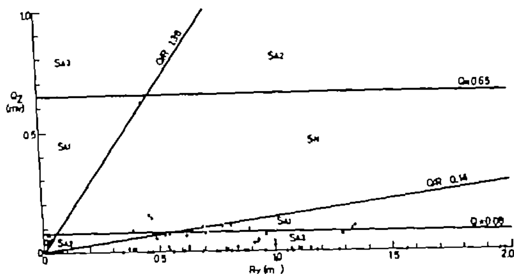


Fig. 5 The combined distribution of the Q and R amplitudes in the Frank Lead Z for 114 infarction patients. The tw oblique lines indicate the upper and lower limits for the normal Q/R ratio, and the tw lines parallel to the abscissa represent the normal limits for the Q amplitude. S_N denotes the area where both Q/R and Q are normal, and S and S_{A1} indicate the areas for abnormal Q/R alone and for abnormal Q alone, respectively I S_{A3} both Q/R and Q are abnormal. It is interesting to note that none of infarction cases is distributed in S_{A3}.

Table II Percentages of subjects in infarction and normal groups whose value under each heading exceeded the respective normal 95 per cent limits in at least one lead

Subjects	Q ampl.	R ampl.	S ampl.	T ampl.	Q/R ratio	S/R ratio	T/R ratio	All 20 items
Infarction patients (114 cases)	64.0	56.1	32.4	72.7	87.6	39.5	64.9*	97.4
Normal series (155 cases)	11.6	12.3	9.7	9.7	12.3	8.4	7.7*	43.8

Ampl. amplitude.
*The T/R ratio in Lead X was not utilized.

clinically applicable type of Q/R norms was attempted. In scatter diagrams of the Q/R in one lead plotted against that of another lead for the normal series there seemed to be no particular relationship observed between any two Q/R ratios with a low correlation coefficient of 0.112 for X ersus Y 0.179 for X versus Y and 0.083 for Y versus Z. This observation seems to favor utilizing three Q/R limits independently determ ned in each lead as the over-all norms for 3-lead Q/R ratios.

In Fig. 6 each becaus value p corresponds to a set of Q/R limits whose three components, that is the limits in Leads X, Y and Z were so determined as to include 100p per cent of the population of healthy men so far as each component is concerned. As the probability density function of the population an exponential distribution was assumed for the Q/R in Leads X and Y and a log normal distribution for Q/R, with satisfactory results of tests of these assumptions (Appendix 2). The ordinate indicates percentages of patients and normal subjects whose Q/R ratio was outside the limits in at least one lead. As p increased that is the limits

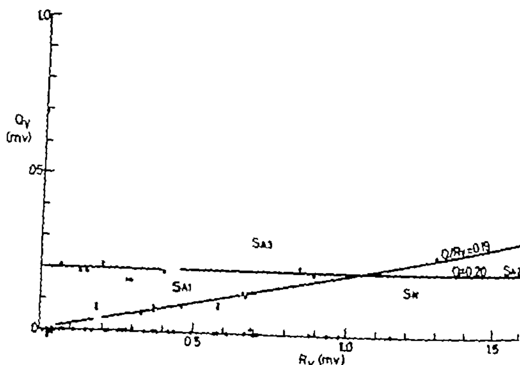


Fig. 4. The combined distribution of the Q and R amplitudes in the Frank Lead Y in 114 infarction patients. The lines Q/R = 0.19 and Q = 0.20 mv represent the normal upper limits for the Q/R ratio and the Q amplitude respectively. Thus the area where both Q/R and Q are normal is denoted by S_N. S_{A1} denotes the area where the Q/R alone is abnormal, S_{A2} the area where the Q amplitude alone is abnormal, and S_{A3} the area where both Q/R and Q are abnormal. It is noteworthy that no infarction case is located in S_{A2}, which means that the Q amplitude is of no further contribution after screening with the Q/R ratio.

important in establishing the diagnostic reliability of the Q/R ratio since infarction patients tended to be distributed across the limit lines.

Fig. 4 shows the combined distribution for Q_y and R_y for infarction patients. In this as well as in Fig. 5, the symbol S denotes the area distribution of both Q and Q/R. The subscript N indicates where these items are within their respective normal limits, whereas areas represented by A1, A2, and A3 indicate (1) abnormal Q/R, (2) abnormal Q, and (3) abnormal Q/R and Q, respectively. Hence the difference between the numbers of cases in S_{A1} and S_{A2} can be a measure of which one of these items is superior to the other. There were no cases seen in S_{A2}, which means no retrieval attained by Q_y in patients with a normal Q/R. The same notation was used in Fig. 5, where Q is plotted against R in infarction patients. Again, no case was observed in area S_{A2}, where Q amplitude alone is abnormal. In Lead X, whose scatter diagram is not shown, only one patient showed an abnormal Q alone.

Thus superiority of the Q/R to the Q amplitude was clearly illustrated and at the same time diagnostic usefulness of the Q amplitude seemed to be disproved. However, the recognition rate for the best discriminator, Q/R, is not satisfactorily high (56.1 per cent). Simultaneous use of all 3 lead Q/R ratios was, then, tried for better discrimination. Application of a three-dimensional rejection ellipse was first considered for determination of the combined normal limit despite its limited clinical applicability due to the complicated calculation involved. This had to be abandoned, however, due to extreme departure from normality observed in the frequency curve of the Q/R in Leads X and Y in the normal series. Then, diagnostic performance of simple combination of the 95 per cent normal limits for the three Q/R ratios was evaluated (Table II). A favorable increase in recognition (87.6 per cent) was observed but was inevitably accompanied by an undesirable increase in the false abnormality in the normal series (12.3 per cent). Therefore, a refinement of

became wide both curves descended as a simple slope but their configurations were quite different. In the interval of p shown in this figure no major change in slope was observed on the curve B for the normal series (false abnormality curve) whereas the curve A for the infarction group (sensitivity curve) consisted of an initial plateau and a steep terminal slope with a transition around p = 0.93. Table III shows sets of 3-lead Q/R limits corresponding to the 7 selected points of p which cover the range of the steep slope of the sensitivity curve. The set of Q/R limits at p = 0.983 is expected to have an acceptable 5 per cent of false abnormality in the population of healthy men if the 3 Q/R ratios are mutually independent. This set is considered not to be different from the set of the limits at p = 0.98 because of rounding procedures in determination of the limits. These rounding procedures may be partly responsible for the stepwise changes for the false abnormality curve.

Discussion

Since Pardee's description there have been numerous conventional electrocardiographic studies concerning the diagnostic importance of Q-wave measurements in myocardial infarction. In vectorcardiographic literature on infarction great emphasis has also been placed on the initial QRS abnormalities, which are the VCG counterpart of abnormal Q waves. The present study with Frank system showed that the orthogonal lead Q measurements were also the most discriminative between the infarction patients and the normal controls and the Q/R ratio was remarkably more discriminative than the Q amplitude in the same lead. Naval and co-workers, using the Frank system, reported that the Q/R ratio showed a significantly higher diagnostic performance in a larger series of infarction patients than the Q duration and amplitude. In the present study T wave measurements were also found to have high sensitivity in infarction patients. However specificity of these measurements in infarction is considered doubtful.

The criteria for differentiation between normal subjects and infarction patients presented in this study were based on the wave-amplitude ratios in the 3 orthogonal scalar leads. Therefore a single-channel electrocardiograph an attachment unit consisting of a lead selector with a resistance network, and a patient cable for the Frank system are sufficient instrumentation for recording. In diagnosis, inspection of the tracings for a rough estimate of the Q/R ratios would probably be sufficient except for borderline cases, in which accurate determination of the ratios would be necessary. Thus, the proposed criteria would have both simple clinical and epidemiologic application. The set of criteria at p = 0.98 in Table III discriminated 77.2 per cent of the infarction patients with negligible false abnormality in normal subjects of approximately 0.6 per cent. The sensitivity of this set compares well with the diagnostic accuracy of ten experienced observers. Of course the sensitivity can be increased to over 90 per cent at the expense of increasing the false abnormality rate in normals (Table III). It is an advantage of the proposed criteria, that they are valid for any infarct regardless of localization.

Age and sex differences have been well recognized in the electrocardiogram and vectorcardiogram. However no significant differences of the mean and variance for the Q/R ratio were observed in each of the Frank-system leads either between normal men and women, or between the two subgroups into which the present series of normal men were classified with a dividing age of 40 years. Pipberger and his co-workers,[11] using the Frank lead ECG's and VCG's of normal men found only weak or insignificant relationships between the Q/R ratio in each lead and age, but showed a significantly smaller mean for the Q/R_x and Q/R in Negroes than in Caucasians. Thus the proposed normal criteria for the Q/R ratios would be applicable to Caucasians irrespective of sex and age but probably would not be satisfactory for race difference.

Although the Q duration has been frequently used for recognition of infarction it has been noted to be of low diagnostic value as compared to the Q/R ratio and was not investigated in this present study

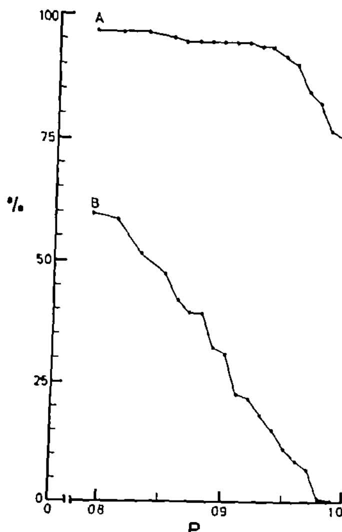


Fig 6 Diagnostic performance of sets of the 3 lead normal Q/R criteria. Every point on the abscissa, *P* has a certain set of the 3-lead Q/R limits defined in Appendix 2 The ordinate indicates percentages of subjects whose Q/R ratio exceeds the limits in at least one lead The curve A represents recognition rates in the infarction series, and the curve *B* false abnormality rates in the normal series.

Table III Seven sets of the three-lead Q/R limits determined on the basis of the respective probability density function assumed for the population of healthy men and the diagnostic performance in 114 infarction patients

Parameters	*P* values						
	0.93	*0.94*	*0.95*	*0.96*	*0.97*	*0.98*	*0.99*
Limits for Q/R ratios							
Lead X	0 to 0.13	0 to 0.14	0 to 0.15	0 to 0.16	0 to 0.17	0 to 0.19	0 to 0.23
Y	0 to 0.17	0 to 0.18	0 to 0.19	0 to 0.20	0 to 0.22	0 to 0.24	0 to 0.29
Z	0.15 to 1.23	0.14 to 1.27	0.14 to 1.33	0.13 to 1.40	0.12 to 1.48	0.10 to 1.64	0.09 to 1.84
Sensitivity in infarction series (114 cases)	93.9%	92.1%	90.4%	85.1%	83.3%	77.2%	73.4%
False abnormality in normal series (155 cases)	18.1%	15.5%	11.6%	9.0%	7.1%	0.6%	0%

The numbers under p values are abscissa values in Fig. 6.

Table A. Results of Fisher's tests of normality for the frequency curves of Frank lead electrocardiographic measurements in 155 healthy men

Parameters	*Lead X*		*Lead Y*		*Lead Z*	
	g_1	g_2	g_1	g	g	g_2
Q amplitude	+1.037 (R)	+0.717 (R)	+1.333 (R)	+1.222 (R)	+1.193 (R)	+2.904 (R)
R amplitude	+0.318 (NR)	−0.161 (NR)	+0.576 (R)	+0.555 (NR)	+1.073 (R)	+1.936 (R)
S amplitude	+1.124 (R)	+1.080 (R)	+1.850 (R)	+3.816 (R)	—	—
T amplitude	+0.422 (R)	−0.240 (NR)	+0.617 (R)	+0.070 (NR)	−0.655 (R)	+1.351 (R)
Q/R ratio	+0.861 (R)	+0.110 (NR)	+0.896 (R)	+0.065 (NR)	+1.214 (R)	+1.324 (R)
S/R ratio	+1.352 (R)	+1.323 (R)	+3.967 (R)	+17.988 (R)	—	—
T/R ratio	+1.170 (R)	+3.842 (R)	+2.332 (R)	+7.618 (R)	—	—

The statistics g_1 and g_2 are measures of skewness and kurtosis of the frequency curve, respectively. If either $tg_1 = g_1/0.195$ or $tg_2 = g_2/0.387$ or both are outside ±1.96, the hypothesis of normality will be rejected at a risk of 5 per cent. The notations (R) and (NR) indicate "rejected" and "not rejected," respectively. See text.

Table B. Results of log normalization for the Q, R, and Q/R in Frank system Lead Z in 155 healthy men

Parameters	*C**	*Mean†*	*SD†*	g_1†	g_2†
Qz	0.117	−0.907	0.344	−0.0004	−0.0088
Rz	0.109	−0.808	0.315	−0.0003	+0.2175
Q/Rz	0.046	−0.695	0.516	−0.0004	−0.3683

*C is the constant in log transformation formula, Y = log (x + c).
†Mean, SD, g_1, and g_2 are all based on log transformed data.

indicated by a positive g_2, and a flatter frequency curve by a negative g_2.

Both g and g for samples from a normal population are distributed normally around zero with a standard error defined by the sample size alone. Hence, the null hypothesis of normality of the population from which a sample of interest was drawn can be tested by entering a normal probability table with $tg_1 = g_1/S.E.g$ and $tg = g_2/S.E.g_2$, where S.E.g and S.E.g are the standard errors of g_1 and g_2, respectively. If $tg = g_1/0.195$ exceeds a range of ±1.96, the null hypothesis is rejected at a risk of 5 per cent in respect to g_1 and the same holds true in case of $tg_2 = g_2/0.387$. Table A shows the results of the tests, which indicate that the hypothesis of normality was rejected on all items except R.

Normalization of the frequency curve was attempted on Q, R, and Q/R in Lead Z for the normal series by employing logarithmic transformation of variates, which was expected to possibly approximate their frequency curves to a normal distribution since the frequency curves showed a mildly positive skewness. The transformation formula is Y = log (X + C) where Y's are transformed values, X's are the original data, and C is a constant. The constant C was determined on trial and error so that the g statistics for the log transformed data, especially g, became as close to zero as possible. Thus quite satisfactory results were obtained (Table B). However, without constant C, that is with C = 0, log transformation of Qz gave an unsatisfactory result with tg = 2.54.

Normalization was also desired on Q/R_x and Q/R_y for the normal control, but their frequency curves were too skewed

There have been many publications on multivariate analysis of electrocardiographic and vectorcardiographic data. Some of these studies were theoretically based on the assumption of a multivariate normal distribution of electrocardiographic items. However, tests of normality performed on the amplitude data of Frank lead ECG's in this normal series seem to disprove such assumptions on many occasions. Appropriate variate transformation may result in favor of such assumption, but difficulties would still remain in Q and S-wave measurements.

Summary

In 114 male patients with a well-documented history of acute myocardial infarction the 3 orthogonal Frank system leads were analyzed for simple, manually measurable indices of infarction. The indices measured were the wave amplitudes of the QRS-T complex and the amplitude ratios of the Q, S, and T to the R wave. The recognition rate of infarction for each item was first evaluated using the 95 per cent normal limits determined from 155 normal men. The Q/R ratio in Leads Z (56.1 per cent) and Y (48.2 per cent), the Q amplitude (43.0 per cent), the T amplitudes and the T/R ratios in Leads X and Y (43.8 to 55.2 per cent) were found to be the most discriminative. The Q amplitude contributed practically nothing after screening with the Q/R ratio. No significant correlation between any two of the 3 lead Q/R ratios was observed. Hence the 3 lead Q/R limits with an equal false abnormality rate in normal subjects estimated from the respective probability density functions were combined to form a set of criteria. The recognition rate in the infarction series and the false abnormality rate in the normal controls of several sets of criteria are presented to allow for arbitrary selection of criteria appropriate to the purpose of screening. The set of Q/R criteria with a false abnormality of 0.6 per cent in normal men has a sensitivity for recognition of infarction of 77.2 per cent. The information necessary for application of this new criteria can be obtained by single-channel electrocardiograph.

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Appendix 1

Fisher's g_1 and g_2 statistics based on k-statistics provide measures of skewness and kurtosis, respectively. If g_1 (or g_2) is zero, there is no departure from normality so far as this measurement is concerned. A positive g_1 indicates asymmetry of the frequency curve with rightward skewness, and a negative g_1 asymmetry with leftward skewness. A frequency curve more peaked than normal distribution is

Physiological correlates of the cardiac thoracic impedance waveform

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When a high frequency sinusoidal current is applied across the chest, changes in the thoracic impedance can be recorded. The thoracic impedance changes consist of deflections composing a waveform. The waveform appears to be related to the mechanical activity of the heart, and has been used to calculate the cardiac output.

The impedance change waveform is complex and little is known about its composition. The purpose of this paper is to correlate the waveform deflections with physiological events.

Materials and methods

The thoracic impedance plethysmographic system used has been previously described and will be summarized here. Four circular flexible metallic electrodes were used: two being placed around the neck, and two around the upper abdomen. One of the inner two electrodes was placed at the base of the neck, the other about 2 cm. below the xiphoid process. The outer two electrodes were separated from the inner ones by about 2 cm.

An activating 6 Ma., 100 kc. sinusoidal current was passed through the outer two electrodes from a constant current source. The inner pair of the electrodes was connected to a high impedance amplifier and associated circuitry to allow determination of the thoracic impedance changes. The resulting impedance change waveform, and its first derivative, were recorded at a paper speed of 50 mm. per second.

Impedance recordings were made on 58 patients. Diagnostic cardiac catheterization studies were done on 55 patients: of these, 6 were normal, 41 had cardiac valvular disease, 3 had congenital septal defects, and 5 had miscellaneous cardiovascular abnormalities. Atrioventricular conduction disturbances were present in 3 patients who did not have cardiac catheterization: 2 had complete heart block, and the other had the Wenckebach type of second degree atrioventricular block.

Results

A typical normal thoracic impedance change waveform is shown in Fig. 1 along with its simultaneously recorded first derivative, the left ventricular pressure, and Lead II of the electrocardiogram (ECG)

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to obtain a satisfactory outcome. Chi square tests were then performed on these items to evaluate goodness of fit to an exponential distribution whose probability density function is

$$f(x) = \begin{cases} \frac{1}{\sigma} \exp\left(-\frac{x}{\sigma}\right) & x \geq 0 \\ 0 & x < 0 \end{cases}$$

where $\sigma = E(x)$ is the population mean Giving $\chi^2 = 5.30$ with degrees of freedom (D F) = 4 for Q/R and $\chi^2 = 4.61$ with D F = 3 for Q/R_y the tests indicated that both Q/R ratios could be considered as a sample from a population of this type of distribution

Appendix 2

The upper and lower Q/R limits (Lu and Lℓ respectively) used *in Fig 6 between* which 100p per cent of the population of healthy men are expected to be included were calculated as follows For Q/R and Q/R_y

$$p = \int_0^{Lu} \frac{1}{\bar{x}} \exp\left(-\frac{x}{\bar{x}}\right) dx$$

where $\bar{x}$ *is the mean value for the ratios in* the normal control and Lℓ was set at 0 For Q/R

$$P/2 = \int_{\bar{x}}^{Lu} \frac{1}{\sqrt{2\pi s}} \exp\left(-\frac{(x - \bar{x})^2}{2S^2}\right) dx$$

$$P/2 = \int_{L\ell}^{\bar{x}} \frac{1}{\sqrt{2\pi s}} \exp\left(-\frac{(x - \bar{x})^2}{2S^2}\right) dx$$

where $\bar{x}$ and s are the mean and standard deviation of the log transformed data for the normal series respectively and Lu and Lℓ are the upper and lower limits also for log transformed values respectively Then these limits were converted to the value in the original unit by the following formulae

$$Lu = e^{Lu} - 0.046$$

$$L\ell = e^{L\ell} - 0.046$$

The 3 lead Q/R limits each of which has the same value p for P were combined to form a set of the limits at P = p in Fig 6.

brachial arterial pulse pressure are also similarly affected by the premature ventricular contraction. These observations are consistent with the known physiological fact that the stroke volume of a premature ventricular contraction is usually less and that of the next beat is usually greater than the stroke volume of the regular beats. An experimental method using the first derivative of the impedance C wave has been devised by which the stroke volume and hence the cardiac output, can be calculated.[2]

The impedance A wave follows the P wave of the ECG as is shown in Figs. 1 and 2. This fact is more easily seen in those arrhythmias where there is a disturbance in atrioventricular conduction. The ECG in Fig. 3 shows the Wenckebach type of second degree atrioventricular block. In this arrhythmia the P-R interval progressively increases until a P wave impulse is not conducted to the ventricles, no QRS complex occurs, and a beat is dropped. The sequence is then repeated. It can be seen that the impedance A wave and the electrocardiographic P wave move together as they shift position in the cardiac cycle. This relationship also pertains in complete atrioventricular heart block, as is shown in Fig. 4.

In contrast to the A wave which is consistently associated with the P wave, the impedance C wave corresponds in timing with the QRS complex of the ECG. The C wave is followed by the V wave in the impedance cardiogram, and the C and V waves occur independently of the A wave. These relationships appear to be consistent regardless of the pathway by which ventricular depolarization is accomplished. This is demonstrated in Fig. 5, which was recorded from the same patient who was presented with complete heart block in Fig. 4. However, the heart is now being paced by a transvenous electrode positioned with its tip in the apex of the right ventricle. The impedance tracing shows the C and V waves follow the pacemaker-produced QRS complexes, and that these waves are independent of the A waves which continue to follow the electrocardiographic P waves.

In atrial fibrillation the ECG does not show P waves, and it would be anticipated that A waves would also be absent in the impedance cardiogram. That this is true is illustrated in Fig. 6. This figure also shows that the amplitude of the C wave and that of its first derivative appear to vary directly with the R-R interval. This is consistent with the above described findings in premature ventricular contractions, and with the use of the impedance waveform in calculating the cardiac output.[3]

Discussion

It appears that the thoracic impedance change waveform provides hemodynamic information. The recording of the imped-

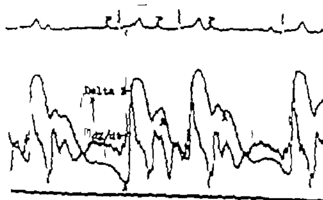


Fig. 3. A recording to show the effect of the Wenckebach type of second degree atrioventricular block. The abbreviations are the same as in Fig. 1. The A waves of the delta Z tracing are associated with the P wa es of the ECG.

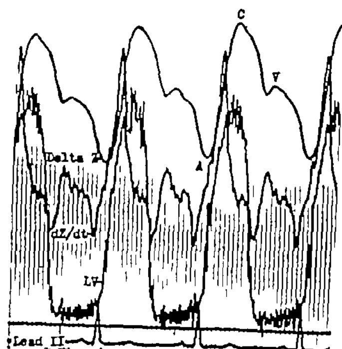


Fig 1 A recording from a patient without cardiac disease. From the top to the bottom, the tracings show the thoracic impedance change waveform (*delta Z*) its first derivative (*dZ/dt*) the left ventricular pressure (*LV*) and Lead II of the ECG Decreasing impedance is upward. The major impedance deflections of the delta Z tracing are marked *A* *C* and *V* The time lines indicate 0 04 second.

A decrease in impedance is shown by an upward deflection The time lines on the abscissa indicate 0 04 second intervals

The largest impedance deflection is upward and is marked *C* in Fig 1 The C wave is immediately preceded by a downward deflection marked *A* and is immediately followed by a second upward deflection marked *V* The upstroke of the C wave is steep but after the peak is reached the downstroke is not as rapid, and is interrupted by the second upward deflection the V wave.

The C wave is a systolic event, since it is synchronous with the QRS complex of the ECG This is confirmed by timing the C wave with the simultaneous recorded left ventricular pressure It can be seen in Fig 1 that the V wave occurs in protodiastole, and the A wave in presystole

The impedance C wave appears to provide hemodynamic information. This is suggested by Fig 2 which shows a premature ventricular contraction followed by a compensatory pause. The amplitude of the C wave associated with the premature beat is smaller and that associated with the postextrasystolic beat is greater than those associated with the regular beats. The first derivative indicates the rate of change of the impedance waveform. The amplitude of the first derivative and of the

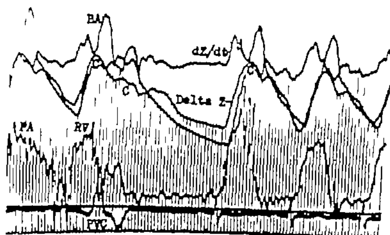


Fig 2 From the top to the bottom the tracings show the brachial arterial pressure (*B A*), the first derivative of the impedance change (*dZ/dt*) the impedance change recording (*delta Z*), a pullback pressure from the pulmonary artery (*PA*) to the right ventricle (*RV*) and Lead II of the ECG The normal sinus rhythm was interrupted by a premature ventricular contraction (*PVC*). See text.

It is interesting to compare the thoracic impedance change waveform with other hemodynamic measurements. It has been demonstrated that the flow of blood in the venae cavae is pulsatile and is similar to that in the pulmonary veins.[5] The flow pattern in these vessels is composed of three major deflections and resembles closely the thoracic impedance change waveform. Following the P wave of the ECG and at the time of atrial contraction the flow of blood in the venae cavae and pulmonary veins slows, or briefly reverses. There then is an increase in blood flow toward the heart coincident with ventricular systole. This is followed by a second acceleration of blood toward the heart in ventricular diastole. These three waves found in the pattern of blood flow in the venae cavae and the pulmonary veins appear to correspond well to the A, C and V waves of the impedance cardiogram. It seems reasonable to speculate that the cardiac thoracic impedance changes may be related to the flow of blood through the venae cavae and/or pulmonary veins, and the heart.

Summary

A high frequency constant sinusoidal current can be passed through the chest by a noninvasive technique and pulsatile changes in the thoracic impedance recorded. These pulsations are related to the beating of the heart. Three major components are present.

One component shows an increase in impedance is associated with atrial contraction and consistently follows the P wave of the electrocardiogram. The other two waves show a decrease in impedance. The first is associated with ventricular systole, and corresponds in time with the QRS complex of the ECG. The systolic wave is then followed by the third component, which also shows a decrease in impedance but occurs in diastole. In instances of arrhythmias the deflection associated with the P wave occurs independently of the other two deflections.

The impedance change waveform is similar to the pattern of blood flow in the venae cavae and the pulmonary veins. It is possible that the impedance changes are related to the flow of blood in these venous circuits, and the heart.

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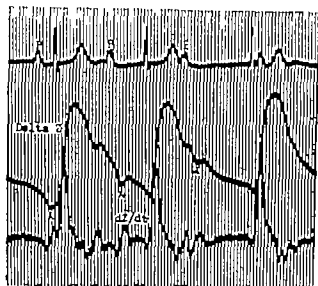


Fig 4 A recording to show complete atrioventricular block. The abbreviations are the same as in Fig 1

ance cardiogram is easily accomplished and has the distinct advantage that a noninvasive technique is used This may be of particular importance when it is desirable to avoid penetration of the skin such as in cardiac transplant patients or space travelers.

The present study shows that the contraction of the atria and of the ventricles are associated with identifiable components in the impedance change waveform Measurements from these recordings can be used to estimate the stroke volume.[8] The impedance cardiogram may also be of value as a continuous monitor of cardiovascular function It is probable that additional applications will be found for thoracic impedance measurements.

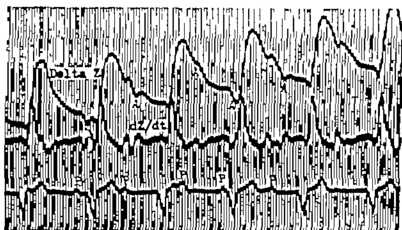


Fig 5 A recording from the same patient shown in Fig 4, who now has an artificial pacemaker

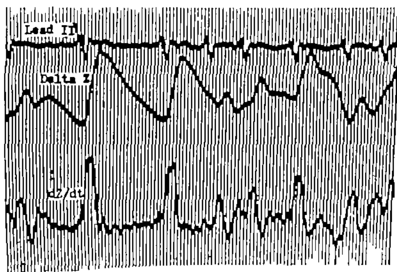


Fig 6 A recording to show atrial fibrillation. The abbreviations are the same as in Fig 1 The P waves of the ECG and the A waves of the delta Z tracing are absent.

tentials across them. Although direct measures of the moment-by moment varia tions across repolarization boundaries have not been possible to date, indirect evidence concerning the geometry of these bound aries can be obtained by observing the behavior of the body surface T wave during alteration of ventricular recovery properties in areas of controlled geometry In the present study alteration of recovery properties was accomplished by irrigating the pericardial sac with saline at a range of temperatures. Although this procedure may have induced changes in recovery proper ties to varying depths of the ventricle dependent on the temperature employed, it is reasonable to assume that the boundary of the area in which recovery times were altered was parallel to the epicardial surface. T wave form during pericardial irrigation was dependent on the geometry of recovery boundaries prior to the procedure and the geometry of the area of altered recovery Since the latter was controlled the findings permitted some conclusions concerning the geometry of repolarization boundaries.

Methods and materials

Experiments were performed on 6 mon grel dogs anesthetized with pentobarbital 30 mg per kilogram The chest was opened with a sternal splitting incision and respira tion maintained with a device which could be halted at a fixed phase of the respiratory cycle. A bipolar stimulating electrode was placed on the right atrial appendage through a small pericardial incision which was ligated to form a fluid tight seal around the electrode wires. The sinus node was crushed through the intact pericardium and the heart was driven from the atrial electrode at a rate which avoided over lapping of P and T deflections. Rubber grommets with attached tubing were in serted into the pericardium through small incisions, and a l p of pericardium ligated around them. Care was taken to avoid producing constricting pericardial bands. The chest cavity was then packed with saline-soaked shredded polyurethane foam which was warmed to body temperature and the chest closed. Such packing has been previously shown to sufficiently restore volume conductor properties of the chest to permit recording of orthogonal ECG leads.[4]

ECG s were recorded using the triaxial lead system designed for the dog and simultaneous orthogonal leads were recorded at a paper speed of 300 mm per second Saline at 4 to 6 temperatures in the range of 20 to 45° C was circulated through the pericardium At each tempera ture the T wave form stabilized after several minutes. At that time respiration was briefly halted at a chosen phase of the respiratory cycle and ECG s were recorded The T wave areas in these records were measured with a planimeter and used to plot mean T vectors on the frontal and horizontal planes and on a rectangular coordinate system.

Results

Examples of T wave alterations induced by pericardial irrigation in one dog are shown in Fig 1 The changes in T wave form are evidence that the experimental procedure altered ventricular recovery times. Temperature has its major effect on the action potential plateau duration with little effect on downstroke configura tion [5] Warming shortens action potential duration and cooling prolongs it. It is reasonable to assume that with pericardial irrigation the boundary of the area in which recovery times were altered paralleled the epicardial surface. The effect of changes in recovery properties on T-wave form were considered in terms of a vector quantity whose magnitude was dependent on the degree of change and whose axis was de pendent on the geometry of the area of induced change. The repolarization vectors originating at the boundary of the area of induced changes were considered to be perpendicular to the line closing the boundary of the area. The vectors were directed from relatively negative to rela tively positive areas that is, they were directed toward the area of altered recovery if recovery times were shortened and away from the area of altered recovery if recovery times were prolonged. The theoretic basis and experimental validity of considering the effect of altered recovery time on T-wave area as a vector quantity

The geometry of ventricular repolarization boundaries

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The time course of ventricular activation and its relation to the QRS complex has been defined in reasonable detail in a number of species and activation sequence maps have been constructed.[1] Comparable maps of ventricular repolarization have not been possible. This is in part due to the lability of repolarization and in part due to the longer time course of repolarization than depolarization. The latter feature of repolarization makes it impossible to map ventricular recovery with the same methods used to map ventricular depolarization.

The most complete study of ventricular recovery to date is van Dam and Durrer's[2] work concerning the intramural distribution of the ventricular refractory period duration. This provides a helpful but limited description of recovery. Refractory period defines recovery in terms of a single stage of that process, namely that at which excitability to a stimulus of specific strength is restored. Van Dam and Durrer found that refractory periods were of the longest duration in the endocardial layers of the ventricles, of shortest duration in the middle layers of the ventricles, and of intermediate duration on the epicardial surface. They inferred that the sequence of functional recovery closely followed the sequence of depolarization in the middle and outer thirds of the ventricles, but did not present their data in map form. A more detailed description of the geometry of repolarization boundaries as well as a description of the recovery process at stages other than that defined by the refractory period are needed. The present study contributes to that description.

Depolarization may be considered in terms of single boundaries of uniform potential whose positions change with time. Repolarization, because of its long time course, is more conveniently considered in terms of multiple coexisting stationary boundaries whose potentials undergo slight variations during the downstroke of the action potential.[3] The form of the T wave of the body surface electrocardiogram (ECG) is dependent on both the geometry of repolarization boundaries and the po-

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*This work was done during the tenure of an Established Investigatorship of the American Heart Association.

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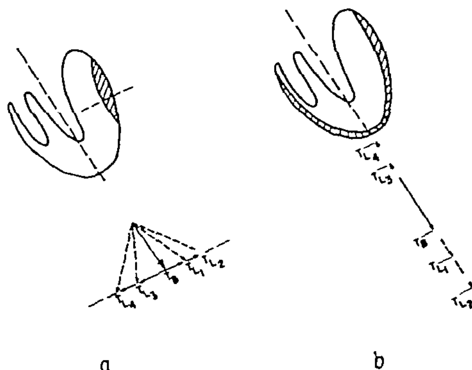


Fig. 2. Diagrams of heart in hich areas of altered recovery time are indicated by the cross-hatching in the left lateral all of the ventricle in part *a*, and the cross-hatching of the entire epicardial surface in part *b*. The effects of different magnitudes of change in these areas on the baseline mean T vectors (T) are illustrated under each diagram. The broken line dra along the long axis of the heart represents the axis of T_B. I both examples the termini of the T ectors after recovery time alteration (T T_{L_4}, T T_{L_1}) fall along an axis that is perpendicular to the line closing the area of altered recovery time. I part *a*, this axis is indicated by the broken line dra through the shaded area on the left lateral wall of the ventricle and in part *b* the axis is the same as the axis of T With progressive shortening of recovery times the ectors T_{L_1} and T_{L_2} mov toard the area of alteration and with progressive prolongation of recovery times the ectors T_{L_3} and T_{L_4} move way from the area of alteration. Each of the T vectors in part has unique axis because the line closing the boundary of altered recovery times is not perpendicular to T and ectors arising at the boundary of this area are directed along an axis other than the axis of T_B. In part *b* all the vectors fall along the same axis because the line closing the boundary of altered recovery times is perpendicular to T and the vectors arising at the boundary of this area are therefore directed along the same axis as T_B.

along the same axis. This would be expected only if the experimental procedure altered recovery properties in an area whose geometry parallels the geometry of recovery boundaries in the baseline state. In one experiment, 3 *a* the regression line did not pass through the 0 point and as indicated on the graph the T ectors had unique axes for each condition of temperature. This ndicates that in this animal the geometry of the area of altered recovery was not the same as the geometry of recovery boundaries in the baseline state.

The same data were plotted on a rectangular coordinate system and are shown in Fig. 4. The three axes of this system are perpendicular to each other. The X, Y and Z coordinates of each point are noted in the parentheses. A rectangular parallelepiped is shown in 4 *a* for perspective. In all of the experiments the termini of the mean T vectors fell along a straight line. With only one exception, illustrated in 4 *a*, mean T vectors in each experiment shared a common axis. This indicates that the geometry of the area of altered recovery paralleled the geometry of repolarization boundaries in the baseline state.

In one experiment (Figs. 3 *a* and 4 *a*) the mean T vector had a unique axis for each condition of temperature. This indicates that in this animal the geometry of

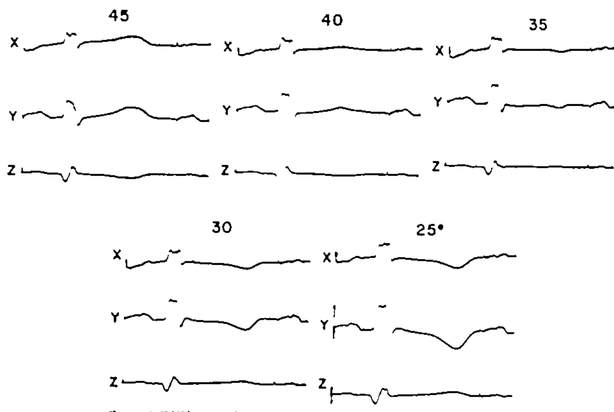


Fig 1 ECG s of a dog taken with the triaxial dog lead system These tracings were taken during pericardial irrigation with saline at temperatures ranging from 25 to 45° C. and illustrate T wave changes induced by the experimental procedure

added to the T area was presented in previous publications[3,7]

Fig 2 illustrates the effect of altered recovery in two different areas In both diagrams the vector T_B has the same magnitude and direction and represents the mean T vector in the baseline state Alteration of recovery times in the shaded areas would introduce repolarization vectors which have been designated local gradient vectors and assigned the symbol T_L. Prolongation of recovery times in the shaded areas would move the termini of the mean T vectors to positions T_{L3} and T_{L4} and shortening of the recovery times would move the termini of the mean T vectors to positions T_{L1} and T_{L2} In both diagrams the termini of the mean T vectors fall along a straight line, but there is an important difference between the states illustrated In Fig 2 *a* the repolarization vectors arising at the boundary of the area of altered recovery indicated by the shading have a different axis than the axis of T_B the mean T vector in the baseline state. As a result each of the T vectors in Fig 2 *a* has a unique axis. In contrast to this situation the geometry of the area of altered recovery in Fig 2 *b* is such that the repolarization vectors arising at this boundary have the same axis as T_B As a result each of the T vectors in Fig 2 *b* has the same axis. The two diagrams are similar in that the termini of T vectors fall along a straight line in both cases. However in Fig 2 *a* each T vector has a unique axis and in Fig 2 *b* all T vectors have the same axis. Alteration of recovery times will result in mean T vectors that have the same axis as the baseline T vector only if a line closing the area of altered recovery is perpendicular to the axis of the mean T vector in the baseline state

Plots of the frontal and horizontal plane T vectors under each temperature condition for all experiments are shown in Fig 3 A regression line for each set of T vectors was calculated and is shown on the graphs. In 5 of the 6 experiments the regression line passes close to the 0 point indicating that all of the T vectors fall

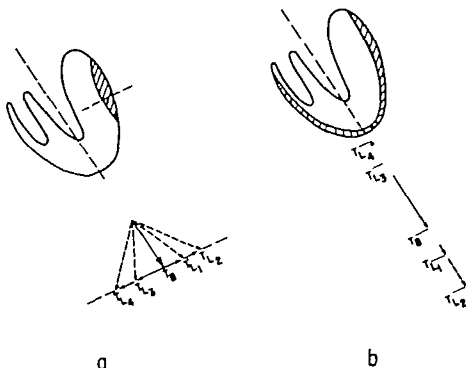


Fig. 2. Diagrams of heart in hich areas of altered recovery time are indicated by the cross-hatching in the left lateral wall of the ventricle in part *a*, and the cross-hatching of the entire epicardial surface in part *b*. The effects of different magnitudes of change in these areas on the baseline mean T vectors (T_B) are illustrated under each diagram. The broken line dra along the long axis of the heart represents the axis of T_B. In both examples the termini of the T ectors after recovery time alteration (T T_{L_2}, T_{L_3}, T_{L_4}) fall along an axis that is perpendicular to the line closing the area of altered recovery time. I part this axis is indicated by the broken line dra through the shaded area in the left lateral wall of the ventricle and in part *b* the axis is the same as the axis of T_B. With progressive shortening of recovery times the ectors T_{L_3} and T_{L_4} mov to- ard the area of alteration and with progressive prolongation of recovery times the vectors T_{L_1} and T_{L_2} move ay from the area of alteration. Each of the T ectors in part has nique axis because the line closing the boundary of altered recovery times is not perpendicular to T and vectors arising at the boundary of this area are directed along an axis other than the axis of T_B. I part *b* all the ectors fall along the same axis because the line closing the boundary of altered recovery times is perpendicular to T and the vectors arising at the boundary of this area are therefore directed along the same axis as T_B.

along the same axis. This would be expected only if the experimental procedure altered recovery properties in an area whose geom etry parallels the geometry of recovery boundaries in the baseline state. In one experiment, 3 *a* the regression line did not pass through the 0 point and as indicated on the graph the T vectors had unique axes for each condition of temperature. This indicates that in this animal the geometry of the area of altered recovery was not the same as the geometry of recovery bound aries in the baseline tate.

The same data were plotted on a rectan gular coordinate system and are shown in Fig. 4. The three axes of this system are perpendicular to each other. The X, Y and Z coordinates of each point are noted in the parentheses. A rectangular parallel epiped is shown in 4 *a* for perspective. In all of the experiments the termini of the mean T vectors fell along a straight line. With only one exception, illustrated in 4 *a* mean T vectors in each experiment shared a common axis. This indicates that the geometry of the area of altered recovery paralleled the geometry of repolarization boundaries in the baseline state.

In one experiment (Figs. 3 *a* and 4 *a*) the mean T vector had a unique axis for each condition of temperature. This indi- cates that in this animal the geometry of

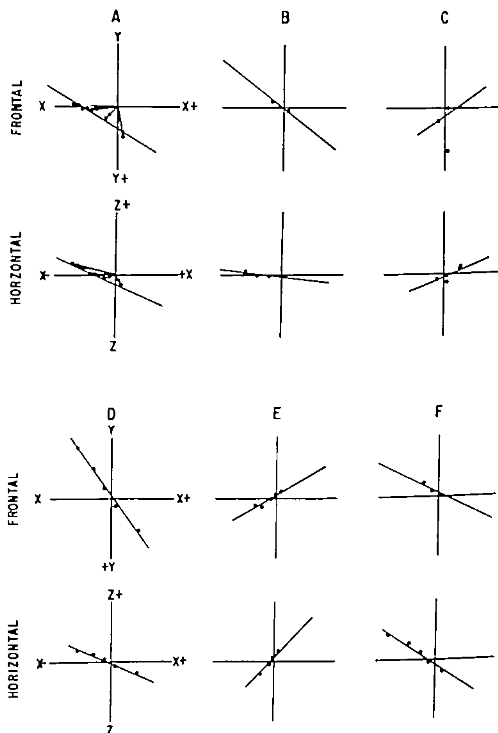


Fig. 3 Horizontal and frontal plane graphs of the termini of T vectors from 6 experiments. The polarity is indicated in parts *a* and *d*. Regression lines have been calculated and these pass close to the 0 point in all experiments except *a*. This indicates that the T vectors shared a common axis. In experiment *a* each T vector had a unique axis as indicated on the graphs. In Fig 4, the same data are displayed on an orthogonal coordinate system, and the temperatures associated with each point are noted.

recovery boundaries in the baseline state did not parallel the geometry of the boundary of altered recovery induced by pericardial irrigation The reason for this finding is uncertain but may be due to an abnormality of recovery in this animal a normal variant of baseline recovery boundaries in the animal or to loculation of irrigating fluid In one other experiment Fig 4 *c* the mean T vector associated with 45° C had a different axis than the other vectors in the same experiment. In this

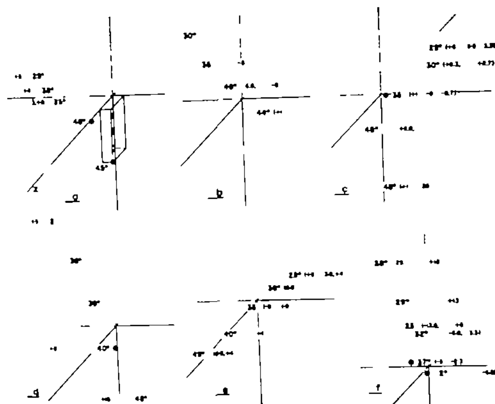


Fig. 4. Graphs of the termini of mean T vectors from 6 experimental animals. The termini of mean T vectors under each of the experimental conditions have been plotted on a rectangular coordinate system. The 3 axes are at right angles to each other and the polarity of the system is labeled in part *a*. A rectangular parallelepiped is shown in part *a* for perspective. The numbers in the parentheses are the projections of the vectors on the X, Y and Z axes, respectively. In each experiment the termini of mean T vectors tended to fall along a straight line and their locations were systematically related to temperature. This indicates that the geometry of the area in which temperature was altered was constant during the course of the experiment. In addition, the axis of the T vectors remained constant in 5 of the 6 experiments indicating the recovery vectors introduced by the experimental procedure were parallel to the baseline T vectors. The exception illustrated in part *e*, shows a unique T axis for each experimental condition. The significance of this is uncertain but may represent a normal variant, an abnormality of recovery or may be due to loculation of pericardial fluid in this animal. In part *c*, when the pericardium was irrigated with 45° C. saline the terminus of the T vector did not fall along the predicted axis. In this animal the configuration of the QRS differed slightly during pericardial irrigation with 45° C. saline from the form of the QRS during the rest of the experiment, and the deviation of the T vector from the predicted position is probably due to secondary T wave changes. In part *f* the termini of T vectors associated with temperatures of 42, 37, 32, 29 and 20° C. were arranged in order but that associated with 25° C. was located between those associated with 32 and 29° C. and may be due to cooling of deeper layers of the myocardium.

case the QRS configuration differed slightly from that associated with other temperatures suggesting alteration of the activation sequence may have been responsible for secondary T-wave changes.

With one exception, the locations of mean T vector termini were systematically related to temperature. The exception Fig. 4 *f* shows T vector termini associated with temperatures of 42, 37, 32, 29 and 20° C located in order on the same axis, but that associated with a temperature of 25° lies between those associated with 29 and 32° C. The 25° value remained on the same axis and is consistent with the interpretation made concerning recovery boundary geometry. The reason for the particular location of this point is not known but may be due to cooling of deeper layers of the myocardium.

Discussion

This study of the geometry of repolarization boundaries is indirect but no entirely satisfactory direct methods of defining these have been devised The sequence of ventricular activation has been mapped in considerable detail and serves to define the sequence of onset of recovery Refractory periods define a particular stage of recovery late in that process and will undoubtedly continue to be useful in the further description of normal and abnormal recovery The present study contributes to a description of ventricular recovery by demonstrating that recovery boundaries throughout the process are sufficiently near parallel to the cardiac surface to account for behavior of the T wave.

It is highly likely that a normal range of recovery boundary geometry exists. One of the experiments in this study showed T wave behavior which was not consistent with recovery boundaries parallel to the cardiac surface Whether this represented a normal variant an abnormality of the recovery process or loculation of pericardial fluid was uncertain

It is well known that ventricular recovery can be thermally altered and T wave changes produced by pericardial irrigation at controlled temperatures have been qualitatively analyzed The major significance of the present study was the particular effect of pericardial irrigation on the axis of mean T vectors If the axis had been altered it would have indicated that repolarization boundaries were not parallel to the cardiac surface but would have permitted no positive conclusion regarding their geometry The axis of mean T vectors remained constant during the course of 5 of the 6 experiments In view of this observation and available information concerning ventricular refractory period distribution it seems justified to conclude that recovery boundaries are sufficiently near parallel to the cardiac surface to account for the behavior of the T wave form

Summary

The effects of altered recovery time in areas of controlled geometry on the T wave form were studied The pericardial sacs of 6 dogs were irrigated with saline at various temperatures in the range of 20 to 45° C T wave form was dependent on the geometry of recovery boundaries prior to alteration of recovery times and the geometry of the area of altered recovery Since the latter was controlled the findings permitted some conclusions about the former In all experiments the termini of mean T vectors fell along a straight line and their positions were systematically related to temperature. This indicated that the area of altered recovery times remained constant during the course of each experiment In addition the T vectors fell along the same axis during the course of 5 of the 6 experiments. This indicated that the geometry of the area of altered recovery times was the same as repolarization boundary geometry prior to pericardial irrigation The one exception may represent a normal variant, an abnormality of repolarization or may be due to loculation of pericardial fluid The results indicated that recovery boundaries are sufficiently near parallel to the cardiac surface to account for T wave form

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Experimental myocardial infarction III Recovery of left ventricular function in the healing phase. Contribution of increased fiber shortening in noninfarcted myocardium

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The recent demonstration that considerable recovery of ventricular function occurs in the healing phase of experimental canine myocardial infarction requires clarification Similar improvement in serial hemodynamic measurements has on occasion been observed in patients following acute myocardial infarction[1-4] One possible explanation for this phenomenon, demonstrated by direct measurements in experimental canine coronary occlusion, is that the aneurysmal bulging of ischemic myocardium present at the onset of infarction gradually disappears due to stiffening of the damaged tissues in the healing phase, thereby presumably resulting in increased effective stroke volume.

The present series of studies was carried out to determine whether additional factors might be responsible for the observed improvement in function. The data obtained indicate that the recovery of over all ventricular performance may be due in part to improved function of the noninfarcted zone of myocardium

Methods

The study was carried out in 15 mongrel dogs weighing 18 to 26 kilograms (mean 22 kilograms) Animals were anesthetized with 30 mg per kilogram of pentobarbital given intravenously and breathed with a Harvard respiratory pump A left thoracotomy and pericardiotomy were performed, and in 10 animals a staged ligation of the left anterior descending coronary artery was carried out as previously described. In the remaining 5 animals, no coronary vessel dissection or ligation was carried out and these served as sham controls. Bipolar pacing wires were sutured to the right atrial appendage and the ends exteriorized.

Animals were allowed to recover from surgery and in the period 4 to 7 days after initial coronary ligation and myocardial infarction, well after postinfarction ventricular arrhythmias had subsided[8] a second procedure was executed. Animals were reanesthetized by giving 1.5 mg per kilogram of morphine sulfate intramuscularly followed by 0.3 ml. per kilogram

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of a mixture containing 200 mg of urethane 50 mg of allobarbital and 30 mg of pentobarbital per milliliter given intravenously Animals were positioned on their left sides and were ventilated with a Harvard respiratory pump

Catheters were placed under fluoroscopic control in the left ventricle and central aorta (retrograde from femoral arteries) and in the right atrium and were attached to Sanborn 267 BC pressure transducers. The zero for pressure measurements was set at the midchest level. A large-bore polyethylene catheter with multiple end holes was inserted through a jugular vein into the right atrium to allow rapid transfusion or withdrawal of blood Left ventricular end-diastolic pressure was adjusted to a range between 5 to 10 mm Hg by withdrawal of blood or by infusion of filtered blood obtained from a donor dog and warmed to 37° C Cardiac output determinations were made using the indicator dilution technique by injecting 2 5 mg of indocyanine green dye into the right atrium and sampling from the central aorta through a Gilford densitometer system During these studies atrial pacing was maintained at rates between 150 and 180 beats per minute in the range previously shown to result in optimal left ventricular performance at the attained levels of ventricular filling pressure [8] Pacing was accomplished using a Medtronics Model 5837 pulse generator Recordings were made on an Electronics for Medicine Model DR-8 recorder

Following measurements of pressure and cardiac output animals were sacrificed by intravenous injection of 10 ml of a saturated solution of potassium chloride. The hearts were rapidly excised and the mitral valve ring and aortic root, including the coronary ostia were sealed off using long curved surgical clamps. Two separate catheters were sutured into the apex of the left ventricle one for pressure measurement, and one for infusion of saline. The ventricle was aspirated with a syringe and then saline was pumped into the ventricle at a rate of 1 6 ml. per second while a pressure recording was made The infused volume could always be recovered at the end of the procedure. For each ventricle a pressure volume curve was constructed by plotting pressure against cumulative volume infused

The left ventricle including the interventricular septum was dissected free from the atria and right ventricle and weighed then the infarct was excised and weighed separately using techniques previously described [7] This procedure was executed in 45 minutes or less to avoid postmortem compliance changes.[10] Infarct size was calculated as a fraction of the left ventricular mass.

Calculations were made as described in the Appendix of fiber shortening fraction in noninfarcted myocardium Fiber shortening fraction may be defined as the fraction of resting or end-diastolic length by which the circumferential fibers of the noninfarcted portion of the ventricle shorten during the ejection phase of systole. The three independent variables in the equation for computing the fiber-shortening fraction (see Appendix) were measured directly infarct size as mentioned above, stroke volume in milliliters by dividing cardiac output in milliliters per minute by heart rate in beats per minute and left ventricular end-diastolic volume from the postmortem pressure volume curve using the left ventricular end-diastolic pressures measured in vivo Since right atrial pressures were normal and were recorded to be in the range of -1.5 to $+2.5$ mm Hg no correction was made for the effect of right ventricular filling on left ventricular distensibility [11] Left ventricular pressures were corrected for intrapleural pressure by observing the baseline shift on opening the chest just prior to termination of the experiment. Left ventricular volumes were normalized to a ventricular weight of 100 Gm Statistical comparisons were made using the Student t test.[12]

Animals with infarcts were arbitrarily divided into two groups those with small infarcts (less than 20 per cent of the left ventricular mass) and large infarcts (greater than 20 per cent of the left ventricular mass) This value was selected because residual hemodynamic abnormalities are usually present in the healing stage of canine myocardial infarction when infarct size exceeds 20 per cent of the left

Table I. Hemodynamic measurements in sham and infarcted animals (mean ± S.E.M.)

Parameter	Sham (No infarct, n = 5)	Small infarct (< 20% LV, n = 5)	Large infarct (> 20% LV, n = 5)
Infarct size (% LV)	0	17 ± 2	28 ± 2
Stroke index (ml./beat/M.²)	34 ± 4	39 ± 3	22 ± 3
Heart rate (beats/min.)	167 ± 11	166 ± 11	156 ± 14
Mean arterial pressure (mm. Hg)	129 ± 13	120 ± 17	116 ± 7
LV end-diastolic pressure (mm. Hg)	6.4 ± 0.9	5.6 ± 0.8	7.8 ± 1.1

LV = Left ventricle.

ventricular mass.[7] There were 5 animals with infarcts in each group.

Results

Hemodynamic measurements. Measurements of pressure and cardiac output in sham-operated animals, and in animals with small and large infarcts are shown in Table I. There were no significant differences between any of these hemodynamic measurements in any of the three groups of animals. Arterial mean pressure was numerically less by 9 mm. Hg in animals with small infarcts than in sham-operated animals, and less by 13 mm. Hg in animals with large infarcts, but the differences were not statistically significant. These results show that all three groups of animals demonstrated a comparable hemodynamic status.

Ventricular volume measurements. The postmortem pressure-volume curves of the left ventricle obtained in this study resembled those previously described.[6] Left ventricular end-diastolic volumes, obtained by applying the in vivo left ventricular end-diastolic pressure measurement to the left ventricular pressure-volume curve obtained at postmortem, are shown in Table II. As noted, the ventricular volumes at comparable ventricular end-diastolic pressures (Table I) are reduced in animals with ligation compared to shams (Table II).

Measurements of the fiber shortening fraction. Calculations of the fiber-shortening fraction for the intact ventricle in sham-operated animals and in the noninfarcted myocardium in animals with ligation are given in Table III. As shown, the value of the calculated fiber-shortening fraction in the residual normal myocardium is significantly increased in animals with large infarcts.

Table II. Left ventricular end-diastolic volume in milliliters per 100 Gm. of left ventricle (mean ± S.E.M.)

Shams	Small infarct (< 20% LV)	Large infarct (> 20% LV)
51 ± 2	36 ± 5	35 ± 4

LV = Left ventricle.
*P < 0.05, compared to shams.

Table III. Fiber shortening fraction in noninfarcted myocardium (mean ± S.E.M.)

Shams	Small infarct (< 20% LV)	Large infarct (> 20% LV)
0.17 ± 0.03	0.22 ± 0.01	0.36 ± 0.07*

LV = Left ventricle.
*P < 0.05, compared to shams.

Discussion

Hemodynamic measurements. The hemodynamic findings in this study are consonant with those previously described in a similar investigation in dogs with healing myocardial infarction. In the latter study the hemodynamic status of animals with

and without infarction was virtually identical except for a raised left ventricular end-diastolic pressure in the group with infarction in those animals with infarct size greater than 20 per cent of the left ventricular mass.[7] In the present investigation left ventricular end-diastolic pressure was brought into the range of 5 to 10 mm Hg by transfusion or withdrawal of blood Transfusion was required in some of the sham-operated animals, and withdrawal of 100 to 200 ml of blood was required in some of the animals with large infarcts. Evidently this intervention did not significantly alter the comparable measurements of stroke index and mean arterial pressure between the three groups

It should be noted that stroke index was significantly reduced in animals with large infarcts (and elevated left ventricular end diastolic pressure) in a previous study from this laboratory[7] This was not true in the present study i e stroke index was well maintained despite the fact that end diastolic pressures were lowered by phlebotomy in this group of animals. There are two possible explanations for this discrepancy (1) Heart rate was not controlled in the previous study[7] and animals with large infarcts tended to have more rapid rates. Hence the reduced stroke index which was observed may have been due in part to relative tachycardia rather than to reduced left ventricular performance (2) Phlebotomy in animals with large infarcts may have induced sympathetic reflex activity which acted to increase contractility in the noninfarcted myocardium Thus it is conceivable though not established that the conditions of the experiment (i e phlebotomy) and the effects thereby reflexly induced may have contributed to the enhancement of fiber shortening in noninfarcted muscle.

Left ventricular end-diastolic volume measurements The seemingly paradoxical finding of reduced left ventricular volumes at comparable filling pressures in ventricles with subacute infarction compared to controls (Table II) has been previously investigated and clarified[6] It has been observed that the ischemic portion of the ventricle becomes stiff and noncompliant several days after infarction showing neither contraction nor appreciable aneurysmal bulging during systole. This stiff portion of infarcted myocardium limits the extent of diastolic filling of the ventricle in the physiologic range of filling pressures, and even more so at elevated filling pressure[6] Reduction of end-diastolic volumes in the infarcted left ventricle does not however imply that the noninfarcted muscle is subjected to a lesser degree of stretch at a given filling pressure than in a normal ventricle since the compliance of this noninfarcted muscle (degree of stretch at a given filling pressure) has been found to be normal[6] Presumably therefore, the Starling mechanism continues to operate in this noninfarcted zone of myocardium in the normal fashion and any observed changes in fiber shortening cannot be explained in terms of alteration in the passive length tension curves of this muscle.

Since ventricular diastolic filling is actually reduced in the infarcted ventricle, this places an additional burden on the noninfarcted fibers with regard to the extent of shortening required to produce a normal stroke volume. From the equations in the Appendix, it will be noted that reduction of end-diastolic volume will require increased fiber shortening in noninfarcted fibers to maintain an unchanged stroke volume.

It has also been pointed out that postmortem end-diastolic volumes measured by the method employed here are smaller than volumes obtained by in vivo cineangiographic methods.[13] However the possible error induced by the postmortem pressure-volume technique does not vitiate the results obtained since all volumes were measured by the same method and presumably any systematic error would be reflected equally or nearly so in all of the determinations of the fiber shortening fraction

The fiber shortening fraction in noninfarcted muscle Computation of the fiber shortening fraction as outlined in the Appendix gives a numerical expression for the degree of circumferential shortening in uninfarcted myocardium The calculation of the fiber-shortening fraction is based upon a number of assumptions, namely that the ventricle is spherical and has a

wall of uniform thickness, that the size of the infarct can be measured accurately and that the infarct comprises a discrete spherical segment of the ventricular wall which behaves in akinetic fashion, that is, neither contracts nor bulges during systole. Justification for these assumptions has been discussed in the Methods section and in previous investigations.[6,7] This calculation probably does indicate directional changes in the parameter in the presence of large infarcts. Nonetheless, because of the many variables involved computation of the fiber-shortening fraction in noninfarcted muscle may be subject to some inaccuracy Indeed the calculated fiber shortening fraction of 0.36 in noninfarcted fibers of ventricles with large infarcts (greater than 20 per cent of the left ventricular mass) probably exceeds the limits which are physiologically possible, although this figure could be explained by presence of infolding of the endocardial layers of the myocardium in end-systole, as noted previously.[14]

Correlations with other observations The mechanism by which increased fiber shortening in noninfarcted myocardium is attained is not known. Metabolic alterations have been described in these noninfarcted fibers,[11,16] but their exact significance is uncertain.

It is possible that myocardial hypertrophy may have already begun to develop in the noninfarcted myocardium within the short time span covered by these studies. It is known, for example, that biochemical and morphological evidence of myocardial hypertrophy may be apparent in the rabbit and rat[18] heart in as little as 2 to 3 days following experimental aortic banding. Also increased connective tissue content of noninfarcted muscle has been described in human hearts, suggesting the presence of hypertrophy.[19] Such changes in the noninfarcted fibers of the ventricle might enable the muscle to display increased shortening, i.e. an increased fiber shortening fraction, when under preloads and afterloads comparable to those in control hearts, as in the present study

Possible presence of hypertrophy does not however lead to any appreciable change in weight of the left ventricle in the type of preparation examined here. In an unreported series of 9 sham-operated and 12 coronary ligated dogs studied under similar conditions (W B Hood, Jr unreported data) the left ventricular weight in grams per kilogram of body weight was 5.1 ± 0.2 (S.E.M.) in shams and 5.4 ± 0.2 (S.E.M.) in coronary-ligated animals and left ventricular weight as a percentage of heart weight was 63.6 ± 3.8 per cent (S.E.M.) in shams and 66.5 ± 2.8 per cent (S.E.M.) in ligated animals. The values do not differ significantly in the two groups. However some of the animals with infarction appeared to have thinning of the ventricular wall in the area of infarction suggesting that loss of muscle in the infarcted area may have been counterbalanced by hypertrophy in noninfarcted muscle thus leading to absence of change in net left ventricular weight.

Significance of the study The results of this study indicate that, to account for maintenance of stroke volume in the presence of small and large myocardial infarcts, with heart rate, ventricular filling pressure and arterial pressure equal or nearly so in all groups studied increased shortening of the noninfarcted myocardial fibers must be implicated

The findings suggest either (1) hypertrophy of uninfarcted fibers, which would allow greater shortening under constant loads due to the greater mass of muscle present, or in the absence of hypertrophy (2) an increase in contractility of uninfarcted fibers, which would result in increased shortening under constant loads in the absence of an increase in muscle mass. In either case the findings provide an additional mechanism to the previously described disappearance of aneurysmal bulging to explain recovery of left ventricular function in the healing phase of experimental canine myocardial infarction

Summary

In the presence of focal myocardial damage stroke volume may be maintained by ventricular dilatation, resulting in an increased left ventricular end-diastolic volume, or by increased fiber shortening in noninfarcted muscle. Relative contribution

of these factors was examined in 5 sham operated and 10 coronary ligated dogs studied 4 to 7 days after surgery Utilizing spherical formulas stroke volume (SV) end-diastolic volume (EDV) and infarct size (IS) as a fraction of the weight of the left ventricle were measured in vivo or at postmortem and the fiber shortening fraction (FSF) in noninfarcted muscle was calculated

$$FSF = [1 - \sqrt[3]{1 - (SV/EDV)}] / (1 - IS)$$

When left ventricular end-diastolic pressure was kept in the range of 5 to 10 mm Hg stroke volume was well maintained in dogs with small (infarct size less than 20 per cent of the left ventricle) and large (infarct size greater than 20 per cent of the left ventricle) infarcts and did not differ from shams However calculation of the fiber shortening fraction gave values of 0 17 ± 0 03 (S E M) for shams 0 22 ± 0 01 for the 5 animals with small infarcts, and 0 36 ± 0 07 for the 5 animals with large infarcts, indicating increased shortening in noninfarcted muscle Left ventricular end diastolic volume was not increased on the contrary the values were 36 ± 5 ml per 100 Gm of left ventricle for animals with small infarcts, and 35 ± 4 ml per 100 Gm of left ventricle for animals with large infarcts compared with 51 ± 2 ml per 100 Gm of left ventricle for shams suggesting that compliance is reduced in infarcted muscle This study shows that hemodynamic compensation in acute myocardial infarction may occur by increased shortening of noninfarcted muscle

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Appendix

Assuming a left ventricle which is spherical and has a uniform wall thickness, and an infarct which is a spherical segment, then Fig 1 represents a cross section through the center of a 25 per cent infarction of the left ventricle. The ratio of circumferential length of infarct to total circumference or $Li/Led + Li$ is identical to infarct weight as a fraction of total ventricular weight. Thus in Fig 1 25 per cent of the circumference is infarcted tissue, and 75 per cent viable myocardium

The following symbols are used in the analysis Ces = end-systolic circumference Ced = end-diastolic circumference Les = end-systolic circumferential length of uninfarcted myocardial segment Led = end-diastolic circumferential length of uninfarcted myocardial segment Li = circumferential length of infarcted segment assumed to be constant EDV = ventricular end-diastolic volume ESV = ventricular end-systolic volume FSF = fraction by which uninfarcted myocardial segment shortens during systole or $(Led - Les)/Led$ IS = infarct size as a fraction of the circumference or $Li\ (Li + Led)$ SV = stroke volume or $EDV - ESV$

Now the following equations apply From the formulas for the volume of a sphere, $V = 4/3\ \pi r^3$ and circumference of a circle, $C = 2\pi r$ the relationship obtains

$$\frac{Ces}{Ced} = \sqrt{\frac{ESV}{EDV}} \quad (1)$$

From Fig 1

$$Ces = Les + Li \quad (2)$$

and

$$Ced = Led + Li. \quad (3)$$

Rearranging the expression for FSF above

$$Les = (1-FSF)\ (Led) \quad (4)$$

Rearranging the expression for IS above

$$Li = (Led)\ (IS)/(1-IS) \quad (5)$$

Rearranging the expression for SV above

$$ESV = EDV - SV \quad (6)$$

Now the following calculations may be made. Substituting equations 2 and 3 and then 5 into formula 1

$$\frac{(Les) + [(Led)\ (IS)/(1-IS)]}{(Led) + [(Led)\ (IS)/(1-IS)]} = \sqrt{\frac{ESV}{EDV}} \quad (7)$$

Multiplying the left hand expression in equation 7 by $(1-IS)/(1-IS)$ and cancelling

$$[(Les)\ \ (1-IS) + (Led)\ (IS)]\ /\ (Led) = \sqrt{\frac{ESV}{EDV}} \quad (8)$$

Substituting equation 4 into equation 8 cancelling and rearranging

$$1 - FSF + (FSF)\ (IS) = \sqrt{\frac{ESV}{EDV}} \quad (9)$$

Substituting equation 6 into equation 9 and rearranging

$$FSF = \frac{1 - \sqrt{1-SV/EDV}}{1 - IS} \quad (10)$$

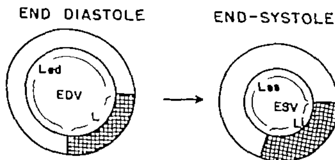


Fig. 1 Diagrammatic representation of cross section of spherical left ventricle with uniform wall thickness in diastole and systole, showing an infarct which comprises 25 per cent of the ventricular mass. For an explanation of symbols, see text.

Equation 10 is a general expression for *FSF* of uninfarcted myocardium incorporating *SV*, *EDV*, and *IS* as variables, all of which were directly measured in this study. For Fig. 1, in which $IS = 0.25$, if representative values such as 20 ml. for *SV* and 40 ml. for *EDV* are employed, then

$$FSF = \frac{1 - \sqrt[3]{1 - (20/40)}}{1 - 0.25} = 0.27$$

The assumption that L_t is constant, that is, that the infarcted muscle is rigid and unchanging in length during systole, derives from previous studies showing that infarcted muscle becomes very inelastic during the healing phase of experimental canine myocardial infarction, showing neither contraction nor expansion during systole.[illegible] To the slight extent that aneurysmal bulging may still exist, the requirements for fiber shortening in noninfarcted tissue would exceed those calculated, and would further accentuate the difference noted in this parameter between animals with and without infarction.

Morphology of a prolapsed posterior mitral valve leaflet

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Prolapse of the posterior mitral valve leaflet is a rare cause of mitral incompetence.[1-4] An illustrative case is presented and the morphologic findings are emphasized, because of the paucity of such information in the literature, as noted by several authors.

Case report

A 63-year-old Caucasian widow had two syncopal attacks in 1962 but no other symptoms until late in 1966 when she began to experience exertional dyspnea. In March 1967 she underwent hysterectomy for menometrorrhagia. While in the hospital, she was told that she had a heart murmur and was placed on digoxin. On this therapy her symptoms improved initially but in succeeding months she experienced increasing dyspnea, orthopnea, paroxysmal nocturnal dyspnea, swelling of the ankles, palpitations, and attacks of precordial chest pain. Early in November 1967 she was admitted to hospital because of severe precordial discomfort that lasted several hours. She responded to rest and diuretic therapy and was subsequently transferred to the Toronto General Hospital for further investigation. There was no history of rheumatic fever.

Significant physical findings were restricted to the cardiovascular system. The pulse was regular except for an occasional premature beat. The blood pressure was 140 systolic and 80 diastolic. Grade 2/4 arteriosclerotic changes were present in the ocular fundi. The ... was es in the jugular ... enous pulse were 3 cm. above the sternal angle. A thrusting left ventricular impulse was palpable in the midclavicular line. The first heart sound was accentuated and the second normally split. A grade 3/6 late systolic murmur was heard maximally at the apex and poorly at the base and in the neck. There was no midsystolic click nor were third or fourth heart sounds audible. The patient had slight ankle edema.

Hematological studies, urinalysis, fasting blood sugar, *blood urea nitrogen, and serum transaminase* were within normal limits. An electrocardiogram showed q waves in Leads II, III and V ... and nonspecific S-T changes in the limb and lateral precordial leads. A chest x-ray revealed slight left ventricular enlargement. Combined right, retrograde, and transseptal left heart catheterization studies showed left and right heart pressures to be normal. Dye curves revealed moderate regurgitation across the mitral valve. This was confirmed in left and right anterior oblique cineangiograms which also demonstrated prolapse of the middle part of the posterior mitral leaflet into the left atrium (Fig. 1). The heart catheterization was uneventful but two days later the patient suddenly developed ventricular fibrillation and died.

At necropsy the heart weighed 340 grams. The

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right chambers and the tricuspid pulmonary and aortic valves were normal The left atrium was dilated. Small areas of fibrosis were apparent in the hypertrophied left ventricular wall particularly near the base of the posterior papillary muscle and in the papillary muscle itself

The mitral valve annulus was 11.5 cm in circumference. The valve had 2 leaflets. The anterior one (*A* in Fig 2) had a semicircular outline, was 4 cm. wide from commissure to commissure, and at its midpoint extended 2.8 cm. into the valve orifice. It had a smoothly nodular surface in the distal half of its auricular surface and was 4 mm. thick near its free edge. The grayish-white posterior leaflet was 7.5 cm. wide from commissure to commissure. It presented as 3 scallops. The anterolateral scallop, near the anterolateral commissure (*B* in Fig 2) extended 1 7 cm. into the mitral orifice the posteromedial commissural scallop (*C* in Fig 2) extended 1.5 cm. while the large middle scallop (*D* in Fig 2) extended 3 cm. Most of the abnormal length of the latter was obvious in the zone where chordae tendineae inserted into the leaflet. This was 2 cm long instead of the usual 5 to 6 mm. (Fig 3). All scallops were thickened slightly but particularly the distal two thirds of the posteromedial commissural and middle ones (up to 5 mm.). The distribution of chordae tendineae to both leaflets and their mode of insertion was normal. However chordae passing to the middle scallop of the posterior leaflet were elongated (3 to 3.5 cm.) and thickened (3 to 4 mm) (Figs. 3 and 5).

Histologically the tricuspid pulmonary and aortic valves were normal. Dense collagenous tissue thickened the auricularis and ventricularis layers in the distal two thirds of the anterior mitral leaflet and the posteromedial and anterolateral scallops of the posterior leaflet. The spongiosa of the lengthened middle scallop was thickened by myxomatous, relatively acellular connective tissue (Fig 4). Also, in the distal two thirds of its length progressively widening bands of connective tissue overlay the auricularis and ventricularis. On the ventricular



Fig 1 Right anterior oblique left ventricular cine angiogram demonstrating prolapse of the middle portion of posterior mitral valve leaflet (outlined by dashed line) into the left atrium during ventricular systole.

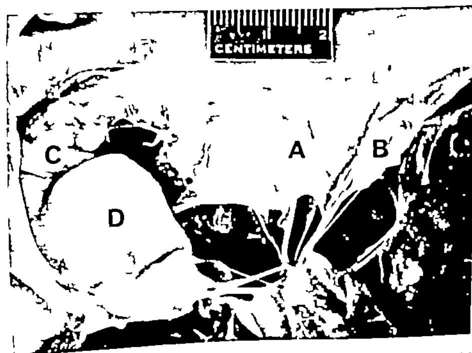


Fig 2. Mitral valve showing abnormal middle scallop of posterior leaflet (*D*). Anterior leaflet (*A*), anterolateral scallop of posterior leaflet (*B*), and posteromedial scallop (*C*) are also seen.

side of the scallop this connective tissue was continuous with that thickening the chordae tendineae. Areas of the fibrosa in this scallop were disrupted by pockets of loosely textured connective tissue, a change that became more obvious as one progressed distally along the scallop. The chordae tendineae to the middle scallop were thickened by dense collagenous connective tissue deposited on their endothelial surfaces (Fig. 5). They did not show myxomatous change.

The patient did not show the stigmata of Marfan syndrome nor were changes of cystic medionecrosis discernible in the aorta or arteries.

Discussion

A late systolic murmur following a mid systolic click may denote mitral regurgitation.[1-4] Of patients who have such a murmur with or without an associated click, a number like the woman reported here have (1) a history of anterior chest pains (2) an electrocardiographic pattern that suggests a posteroinferior myocardial infarction or ischemia and (3) a posterior mitral valve leaflet that balloons into the left atrium during systole to produce a distinctive appearance in cineangiograms.[4] However not all patients with a prolapsed posterior mitral valve leaflet present every feature of the syndrome.

The myxomatous segment of posterior leaflet in our patient was far less cellular than the two described by Fernex and Fernex[6] as examples of "la dégénérescence mucoïde des valves mitrales"; both patients had mitral insufficiency. On the other hand the changes closely resemble those defined by Reid and associates in five patients and by Bitter and Sousa in another three all of whom had mitral insufficiency.

Some of the patients with this condition have Marfan's syndrome[7] or a forme fruste of that condition. Such a congenital lesion explains the familial incidence of prolapsed mitral leaflets noted by some authors.[1,2,9] However other patients[7,9] like ours have neither the stigmata nor a family history of Marfan's syndrome. In them the cause of the myxomatous degeneration is not apparent. Possibly it represents a degenerative change. For example, Pomerance,[11,12] who studied the effects of age in human hearts, found that a morphologically comparable metachromatic degeneration could cause local ballooning of a leaflet, or if severe mitral leaflet ectasia and prolapse. In her experience severe changes were uncommon and not related to the patient's age but lesser degrees were frequent and their incidence increased with age. Alternatively the myxomatous leaflet degeneration might

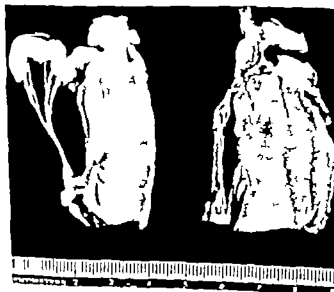


Fig. 3. Comparison of sectioned abnormal middle scallop of posterior mitral leaflet (left) from this patient with that from [...] oman of the same age without mitral insufficiency but with left ventricular hypertrophy



Fig 4 Midzone of middle scallop of posterior mitral leaflet, auricular surface uppermost. Note myxomatous tissue in spongiosa (*S*) and disrupting fibrosa (*F*) connective tissue (*C*) thickens, auricularis (*A*) and ventricularis (*V*). (Hematoxylin and eosin. × 40.)

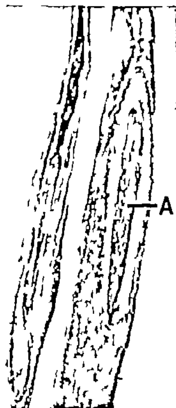


Fig 5 Connective tissue coat thickening chordae tendineae (*A*) passing to abnormal middle scallop of posterior mitral leaflet. (Hematoxylin and eosin. × 40.)

result from the action of a noxious agent. Similar changes occur in the cardiac valves of rats fed beta aminopropionitrile.[13]

We suspect that the leaflet changes precede the chordal ones and that as the leaflet billows an inevitable result of ventricular pressure the chordae lengthen In our patient the chordae were thickened a finding at variance with the thin elongated chordae described by Barlow and associates[4] in one patient. Unfortunately Barlow and associates give no further histological details. Pomerance[13] also observed attenuated chordae associated with myxomatous mitral valve leaflets. Possibly the chordal thickening in our patient was an effect of hemodynamic changes in the ventricle or represents some other secondary effect. The chordae did not show the myxomatous change described in three patients by Bitter and Sousa.[3]

Myxomatous change may affect the aortic as well as the mitral valve leaflets.[7] In our patient the myxomatous transformation was associated with prolapse, but other presentations occur A myxomatous leaflet may rupture as in the case reported by Edynak and Rawson.[14] Recently O Brien and associates[15] described the sudden onset of aortic incompetence secondary to ruptured aortic valve leaflet in two adult males neither of whom had the stigmata of Marfan s syndrome. Both leaflets showed myxomatous change.

The O Brien group did not mention any operative difficulty in replacing the valve with a prosthesis. However Reid and associates[7] found that their patients with a supposed forme fruste of Marfan s syndrome tended to disrupt suture lines and did not form normal scar tissue. This difference in behavior further emphasizes the need to define the pathogenesis of the myxomatous change for different causative mechanisms may dictate different methods of treatment.

A study of the anatomy of the normal mitral valve in progress at the Department of Pathology, Banting Institute[16] showed that 46 of 50 posterior mitral leaflets from adult hearts had 3 scallops. In 42 instances the posterior leaflet had a large middle scallop with smaller comparably sized anterolateral and posteromedial commissural scallops. Either a posteromedial or an anterolateral scallop was the largest in the other 4 hearts. In the present report, our patient had a myxomatous middle scallop (Fig. 2) which prolapsed into the left atrium and could be seen in the midzone of the posterior leaflet area in the right anterior oblique cineangiogram (Fig. 1). This appearance differs from that shown by Stannard and associates[3] in figs. 7 and 8 of their paper where the shadow of the prolapsed leaflet is seen at the edge of the posterior leaflet area. In our opinion the shadow in their case was caused by a prolapsed posteromedial commissural scallop. These observations suggest that in the future it may be possible to recognize whether one or more scallops of the posterior leaflet protrude into the left atrium in cases of mitral leaflet prolapse.

Summary

A case of prolapsed posterior mitral valve leaflet in a 63-year-old woman is presented. Morphologically the middle scallop of the leaflet was lengthened and showed myxomatous change. Chordae tendineae to the scallop were thickened. A brief discussion of the possible pathogenesis of this change is included and attention drawn to the possibility of recognizing in cineangiograms whether one or more scallops of the posterior leaflet have prolapsed.

The authors thank Dr. Harry Shanoff for referring this patient, Dr. Harold E. Aldridge for carrying out the heart catheterization and cineangiographic studies, and Professor A. C. Ritchie, Mrs. M. Lorber and Miss U. Sodtke for their assistance in the preparation and review of this manuscript.

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Demand pacing and carotid sinus syncope

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A hypersensitive carotid sinus reflex is a common cause of distressing and disabling symptoms in the middle-aged and elderly patient. Medical surgical and roentgenologic treatment of this condition has been suggested but to date none has been completely satisfactory The primary manifestation of this disease which may cause injury or sudden death to the patient are unheralded syncopal attacks

Cardiac pacing with transvenous or myocardial electrodes is the treatment of choice for syncope due to complete heart block [1-4] The treatment of recurrent syncope due to carotid sinus sensitivity with a demand pacemaker is a new therapeutic approach and has not been previously reported

Case report

An 81 year-old woman was admitted to the St. Joseph s Hospital in Marshfield on Nov 6 1968, because of recurrent episodes of lightheadedness and syncope, which had occurred since 1964 she had arteriosclerotic heart disease with atrial fibrillation for which she was digitalized in 1967

Physical examination revealed an irregular pulse averaging 84 beats per minute and blood pressure of 160/90 mm. Hg The carotid pulses were of good quality and no cervical bruits were heard. The lungs were clear to percussion and auscultation and the heart was not enlarged. There was a Grade 2/6 apical systolic murmur The abdominal examination was not remarkable. The peripheral pulses were adequate and the neurologic examination was negative A chest roentgenogram was normal. An electrocardiogram revealed atrial fibrillation.

Laboratory studies showed the following white blood cells, 7 700 per cubic millimeter differential, normal hemoglobin, 14 7 grams per cent hematocrit 46 per cent urinalysis, negative for sugar and albumin, specific gravity 1 007 blood sugar 127 mg. per cent blood urea nitrogen, 16.5 mg per cent, cholesterol, 204 mg per cent calcium, 10.2 mg per cent and inorganic phosphorous, 2.6 mg per cent.

After momentary carotid sinus pressure on the left, the patient had a period of asystole lasting 3.5 seconds, which was associated with transient syncope. After similar carotid sinus pressure on the right, an asystole of 1.5 seconds duration occurred (Fig 1). The patient was placed on tincture of belladonna, 12 drops 4 times daily and sublingual Isuprel, 10 mg every 4 hours. These therapeutic measures, however did not influence the carotid sinus sensitivity

On Nov 12 1968 a biopolar endocardial electrode was placed in the right ventricle via the right external jugular vein and connected to a demand pacemaker implanted in the soft tissue below the right clavicle (Chardack-Greatbatch Implantable Demand Pacemaker System, Medtronic, Inc., Minneapolis, Minn.) Subsequent massage of either carotid sinus continued to produce periods of asystole. With a 1 second delay however the pacemaker began to stimulate the myocardium at a rate of 60 impulses per minute and the patient remained asymptomatic (Fig 2). She was discharged from the hospital on the seventh day following pacemaker implantation in excellent general condition. In the brief follow-up period, the patient has remained asymptomatic and no further spells of dizziness or syncope have occurred.

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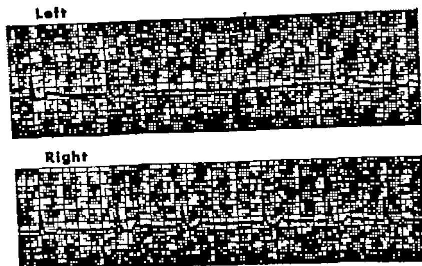


Fig. 1 Carotid sinus massage followed by asystole.



Fig. 2. Carotid sinus massage following placement of demand pacemaker. Asystole prevented by pacemaker stimulation (continuous tracing).

Discussion

Hypersensitivity of the carotid sinus was first described in 1930 by Roskam.[6] The most common symptoms of this syndrome are vertigo, syncope, focal neurologic attacks and mental changes. The central nervous symptoms are generally attributed to cerebral ischemia. Weiss and Baker[7] in 1933 noted that Adams-Stokes attacks could be induced by stimulation of a hypersensitive carotid sinus. They stated that the most frequent electrocardiographic abnormalities are impaired conduction and abnormal rhythm. Heron and associates[8] discussed the association between carotid sinus syncope, cardiac arrhythmia, hypotension and myocardial infarction. Arteriosclerotic heart disease has been recognized as a conditioning factor for the circulatory response to carotid sinus pressure[9] and a high incidence of carotid sinus sensitivity in persons with documented extracranial carotid artery occlusive disease was described.[11] Tuckman and associates[12] believe that carotid sinus syncope is frequently produced by a reduction in cerebral blood flow occurring as the result of partial or complete occlusion of an internal carotid artery on the side of the carotid sinus pressure. Thomas,[13] in a recent review distinguished between a hyperactive carotid sinus reflex and carotid sinus syncope.

The medical treatment of carotid sinus hypersensitivity with syncope consists of anticholinergic or sympathicomimetic drugs to block the circulatory effect of the carotid sinus reflex. Belladonna has proven to be the most useful drug. In severe cases, surgical denervation of the effected sinus has been recommended but this form of treatment is not always successful. Spontaneous remission may also occur. Roentgen therapy was introduced as treatment for carotid sinus hypersensitivity by Stevenson[14] in 1939. Good response to this

Demand pacing and carotid sinus syncope

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A hypersensitive carotid sinus reflex is a common cause of distressing and disabling symptoms in the middle-aged and elderly patient. Medical, surgical, and roentgenologic treatment of this condition has been suggested, but to date none has been completely satisfactory. The primary manifestation of this disease which may cause injury or sudden death to the patient are unheralded syncopal attacks.

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On Nov. 12, 1968, a bipolar endocardial electrode was placed in the right ventricle via the right external jugular vein and connected to a demand pacemaker implanted in the soft tissue below the right clavicle (Chardack-Greatbatch Implantable Demand Pacemaker System, Medtronic, Inc., Minneapolis, Minn.). Subsequent massage of either carotid sinus continued to produce periods of asystole. With a 1 second delay, however, the pacemaker began to stimulate the myocardium at a rate of 60 impulses per minute and the patient remained asymptomatic (Fig. 2). She was discharged from the hospital on the seventh day following pacemaker implantation in excellent general condition. In the brief follow-up period, the patient has remained asymptomatic and no further spells of dizziness or syncope have occurred.

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type of treatment was reported by others after the conventional drug treatment had failed[18] but the results are unpredictable

Long term electrical stimulation of the heart has become the accepted treatment of choice for symptomatic heart block as well as for syncope due to sinus bradycardia or other arrhythmias. The transvenous route of cardiac pacing has been recommended for the elderly or seriously ill patient.[3,4,16,19] Fixed rate pacing is being used for the treatment of symptomatic complete heart block In intermittent heart block or sinus bradycardia fixed rate pacing causes competition between normally conducted and pacemaker induced heart beats This may lead to repetitive beats, ventricular tachycardia and ventricular fibrillation[20]

The demand or standby pacemaker is used in patients who have a predominantly normal sinus rhythm and have only intermittent episodes of symptomatic complete heart block bradycardia or asystole.[21] The pacemaker responds to the absence of a QRS potential at the electrode terminals and ventricular depolarization inhibits the pacemaker output for a controllable time[22,23] In the case presented here an output delay of 1 second was used Prolonged asystole due to carotid sinus stimulation could be prevented by electrical cardiac pacing

Demand pacing appears to be the safest and a most effective immediate form of treatment for recurrent syncope due to carotid sinus hypersensitivity Using the intravenous catheter electrode the procedure is safe and well tolerated

Summary

This is a report of a new treatment for syncopal attacks due to carotid sinus hypersensitivity The successful treatment with a demand pacemaker using a transvenous electrode catheter is described This case demonstrates that demand pacing appears to be the treatment of choice for this condition The medical surgical and roentgenologic treatments are also discussed.

The authors are indebted to Dr William O Myers for the pacemaker placement in this patient.

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Table I. Cardiac catheterization data

Parameters	April 9, 1959		Sept. 14, 1966		Aug. 1, 1967
	O_2 sat.	Pressure	O_2 sat.	Pressure	(Operation)
SVC	—	—	75	10 6, mean 6	
RA	61	22/16	75, 72	4 y 4	
IVC	69	—	76		
RV	73	70/8	73, 73	90/0*	40/5
MPA	79	60/20	75	30/10	38/16
L(R)PA	82	—	73, 74	18/8	
LA	—	24/12	—		
LPAw	—	—		12/8, mean 10	
LV	—	85/8	99	112/5*	
FA	96	—	97	110/65	105/60

Abbreviations: SVC, superior vena cava; RA, right atrium; IVC, inferior vena cava; RV, right ventricle; MPA, main pulmonary artery; L(R)PA, left or right pulmonary artery; LA, left atrium; LPAw, left pulmonary artery [illegible] pressure; LV, left ventricle; FA, femoral artery.
*Simultaneous pressures.



Fig. 1. Electrocardiogram, external phonocardiogram from the second intercostal space at the left sternal border, internal phonocardiogram from the right ventricle under the pulmonary valve, and right ventricular pressure.

Spontaneous closure of ventricular septal defect following pulmonary artery constriction (banding)

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Banding of the pulmonary artery is a well-established palliative treatment for ventricular septal defect causing heart failure in infancy. Reconstruction of the pulmonary artery and closure of the ventricular septal defect after pulmonary artery banding has been reported by Dammann and colleagues,[3] Dobell and associates,[5] Hallman and colleagues,[8] Vince[18] and others. Although spontaneous closure of ventricular septal defect is well known[1,2,4,7,9,12,13,17] there is only one case reported in which this has occurred after pulmonary artery banding (Edgett and colleagues[6]). Our experience with pulmonary artery banding is reported elsewhere (Stark and colleagues[14]). Twenty-four patients with ventricular septal defects and pulmonary artery banding have had total corrective operations. In one of these patients the ventricular septal defect had closed spontaneously.

Case report

Patient A. W. was born of a normal delivery with a birth weight of 7 lb. 12 oz. At 2 weeks of age he became dyspneic and began to feed poorly. At one month of age he was admitted to this hospital with a diagnosis of congenital heart disease and congestive heart failure. His weight at this time was 8 lb. 2 oz. A loud pansystolic murmur was heard at the lower sternal border with a mid-diastolic murmur at the apex. The second sound was loud in the pulmonary area. The liver was palpable three-finger breadths below the left costal margin. Chest x-ray showed cardiac enlargement with increased pulmonary vascularity; the electrocardiogram showed a mean frontal QRS axis of −170 degrees, right ventricular hypertrophy, and right bundle branch block.

He was treated with digoxin and improved. During the next 6 months he was admitted twice to hospital because he was unable to feed adequately. On the second of these admissions, when he was 7 months old, cardiac catheterization was performed (Table I). This showed a left-to-right shunt at ventricular level with a pulmonary to-systemic flow rate ratio of 2 to 1 approximately. There was pulmonary hypertension.

Pulmonary artery constriction was therefore performed. At operation a fibrosed ligamentum arteriosum was found. The pulmonary artery pressure was 60 mm. Hg systolic and the pulmonary artery was constricted until the pressure distal to the band was 30 mm. Hg systolic. His postoperative course was uneventful and he was discharged from hospital 9 days after operation.

His condition improved, and one year after the operation digitalis was discontinued. An ejection systolic murmur in the pulmonary artery area continued to be audible. He was reviewed as an out-patient each year. At the age of 8 years he was readmitted for assessment prior to corrective surgery. He had no symptoms and weighed 50 lb. Intracardiac phonography (Fig. 1) confirmed that the second sound was widely split, the pulmonary element being delayed. There was a loud ejection systolic murmur in the pulmonary area.

Chest x-ray. The heart was normal in size and the lung vascularity was normal.

Electrocardiogram. First degree A-V block with moderate right ventricular hypertrophy was seen.

Cardiac catheterization. This showed no evidence of intracardiac shunts (Table I). There was right

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phied muscle of the septum, so that toward the end of systole the ventricular septal defect would be effectively closed. Binding of the septal leaflet of the tricuspid valve across defects of the membranous septum has been observed at necropsy and during open-heart surgery.[1,2,4,13] Evans and colleagues[7] have suggested that the defect could be progressively narrowed by hypertrophy of the muscle of the interventricular septum and become completely closed by apposition of the margins. Fibrous tissue proliferation, due to turbulent blood flow or endocarditis, has been suggested as a further mechanism which may lead to closure of the defect.[1,6,12,13]

Spontaneous closure of small ventricular septal defects has been well recognized and occurs frequently. The suggested incidence varies from 12 to 30 per cent (Bloomfield, Nadas and colleagues,[11] Evans and colleagues,[7] and Olin[12]). Large defects causing heart failure are less likely to close spontaneously, but this has been reported.[4,7,10,11,17] The ventricular septal defect in our patient was large enough to produce congestive heart failure in the first months of life. The diagnosis was confirmed by cardiac catheterization. Medical therapy was not effective so the pulmonary artery was constricted at the age of 7 months. The defect could not be detected either by cardiac catheterization or angiocardiography 7½ years later. Pulmonary artery stenosis was subsequently relieved on cardiopulmonary bypass with a good result. Whether the pulmonary artery constriction (banding) influenced the spontaneous closure of the ventricular septal defect remains to be proved.

Summary

A case of spontaneous closure of ventricular septal defect after pulmonary artery constriction (banding) is presented. The pulmonary artery was constricted at the age of 7 months for intractable heart failure. Seven years later no ventricular septal defect could be detected using cardiac catheterization and biventricular angiocardiography. The pulmonary artery was reconstructed on cardiopulmonary bypass with a patch of pericardium. Direct auscultation over the right ventricle and diagnostic pressures were normal. The patient is well 14 months postoperatively.

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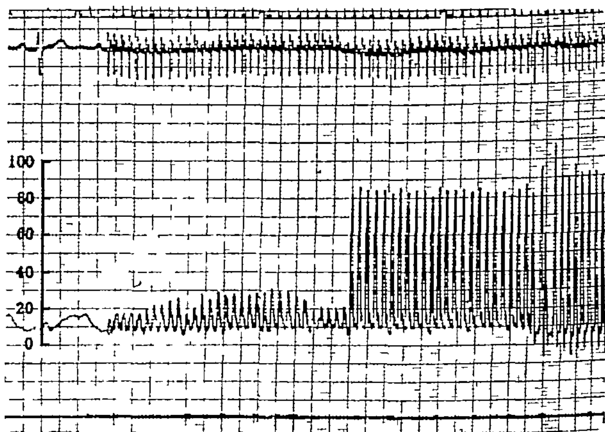


Fig 2 Withdrawal pressure trace from the main pulmonary artery across the constriction to the right ventricle.



Fig 3 Lateral angiocardiogram, right ventricular injection. Constriction demonstrated on the main pulmonary artery

ventricular hypertension with supravalvar pulmonary stenosis (Fig 2).

Angiocardiography Both left ventricular and right ventricular biplane Elema angiocardiograms and left ventricular cineangiography showed no evidence of ventricular septal defect. There was a tight constriction of the main pulmonary artery (Fig 3)

Operation Aug 1 1967 On cardiopulmonary bypass the pulmonary artery was incised longitudinally across the band, and a patch of pericardium 2 5 by 2 cm. was sewn into the incision with continuous 5-0 silk Bypass was discontinued and diagnostic pressures were taken (Table I). Right ventricular pressure was 40/5 pulmonary artery pressure 38/16 with systemic pressure 120/80. There was no murmur on auscultation over the right ventricle.

The postoperative course. This was uneventful and the patient was discharged from the Hospital on Aug 27 1967 He was last seen 14 months after the operation. His general condition was excellent. A short Grade 2 ejection systolic murmur was audible in the pulmonary area.

Discussion

The mechanism of spontaneous closure of ventricular septal defects is open to question. Hoffman and colleagues[4] believe that ventricular septal defects could be occluded by contraction of

2 per high-power field occasional red blood cells. Platelets on admission were 25 000 per cubic millimeter bleeding time, 6 minutes (normal 1 to 5 minutes) partial thromboplastin time, 74.3 seconds (normal less than 60) clotting time, 22 minutes (normal range, 6 to 20).

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Admission prothrombin showed one-stage, 42 per cent of normal two-stage, 50.2 per cent of normal, partial thromboplastin time, 85.3 seconds prothrombin consumption, 89.2 per cent of normal. Clot retraction was 36.0 per cent (normal range, 30 to 50 per cent). Fibrinolysis was 44.0 per cent (normal *5 per cent in 24 hours*). The serum glutamic oxalacetic transaminase was 25 U serum lactic dehydrogenase, 340 U alkaline phosphatase, 0.7 U The bilirubin (total) was 0.9 mg per cent w th direct fraction of 0.4 mg per cent. An electrocardiogram revealed sinus tachycardia with diffuse nonspecific ST T–wave changes thought to be due, in part, *to the fast* rate. Serum electrophoresis showed 7.9 gm. per cent protein with all constituents within normal range. Bone marrow aspiration revealed an activ marrow th an M F ratio of 3.1 Megakaryocytes ere present. Orderly myeloid maturation, erythroid hyperplasia, normoblastic maturation, basophilic retention, eosinophilia, and absent stainable iron ere noted.

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Chest x-ray revealed *minimal* scoliotic curv of the dorsal spine ith free pleural fluid bilaterally extensiv pleural thickening on the right with notching of the ribs, and enlargement of the heart ith considerable atelectasis of the right lung

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On physical examination the pulse rate was rapid at *120* per minute. No findings of systemic congestion were present. The boy was thin and appeared chronically ill. He used accessory respiratory muscles in dramatic fashion No murmur was heard. Heart tones were distant. It was felt that the absence of systemic congestion tended to exclude acute forms of pericardial or myocardial disease as an explanation of the *patient s grossly labored respirations*. The auscultatory findings excluded valvular heart disease A chronic constrictive pericarditis was unlikely unless it were postulated that a selective constriction of pulmonary veins was the cause of significant pulmonary venous hypertension. Chronic constrictive pericarditis is defined as a degree of pericardial thickening sufficient to impede diastolic filling of the ventricular chambers. This definition must be emphasized since the mere finding of a thickened pericardium even of gross magnitude, does not by necessity imply the hemodynamic consequence of an imped ment of ventricular filling

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Case report

Clinical abstract The patient an 11 year-old Caucasian male student had a long history of upper respiratory infections and asthma. He was delivered normally at term as the youngest of four siblings. Birth weight was 9 pounds, 8 ounces. He had a fractured clavicle at 18 months following a fall. Glasses were required at the age of 1 year because of myopia One sister had asthma. He was first thought to have recurrent asthma at 7 years of age. He had no known allergies and the asthma was attributed to infection. He had not received chronic therapy but had been treated symptomatically for each episode In 1963 he had pneumonia complicated by empyema which subsequently required decortication of the right lung

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Hospital course Following admission the patient continued to experience wheezing although the respiratory status became somewhat stabilized. Multiple abnormalities in coagulation of the blood were noted These included increased bleeding time, reduced prothrombin time prolonged partial thromboplastin time decreased prothrombin consumption, and a decrease in platelets and fibrinogen level. An accelerated euglobulin lysis and evidence of fibrin products in the serum were also noted. Quantitative immunoglobulin studies revealed an increase in IgG (26 mg per milliliter), slightly decreased IgA (1.5 mg per milliliter) and a normal IgM (1 4 mg per milliliter). Numerous skin tests were done to detect an allergic tendency as well as evidence of infections such as blastomycosis, coccidiomycosis, or histoplasmosis. All skin tests were negative. Heparin was administered to treat the apparent consumption coagulopathy It was thought that the affected lung might require decortication or removal if it was functioning as a hemangioma providing a locus for sequestration of platelets. Coagulation studies showed some improvement following heparin administration and, on April 3 1968, bronchoscopy with topical anesthesia was done. During this procedure he had severe bleeding from the tracheobronchial tree and cardiac arrest with immediate resuscitation following closed-chest massage and intravenous bicarbonate. Subsequently he experienced continued bleeding from the trachea despite the administration of fibrinogen and died several hours later approximately two weeks following admission.

Laboratory data Admission hematology revealed hemoglobin, 11 9 white blood count, 5,900 with a differential count of 78 polys, 1 band, 14 lymphocytes, 7 monocytes, and 1 eosinophil. The hematocrit was 34 Admission urinalysis showed pale, yellow clear urine specific gravity 1.027 pH 6.5 no protein or sugar white blood cells, *0 to*

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Fig. 3. This portable roentgenogram, made following cardiac arrest on April 3, 1968, show subcutaneous emphysema with increased pulmonary density on the left and increased pleural fluid bilaterally.

disordered coagulation involving all stages of the coagulation mechanism. Furthermore, the history suggested that the coagulation abnormality was an acquired one inasmuch as there was no history of a bleeding diathesis until 4 months prior to his admission. He had tolerated major thoracic surgery *with lung* decortication at age 7 with no evidence of bleeding. The family history was also negative for a bleeding disorder. These findings make a congenital genetically conditioned abnormality of coagulation very unlikely. Examination of the bone marrow revealed normal marrow cellularity with normal numbers of megakaryocytes. Erythroid hyperplasia was present and stainable iron was absent. These findings were interpreted as excluding disorders such as aplastic marrow disease, leukemia, and deficiency diseases due to B_{12} or folic acid. Although the findings did not rule out idiopathic thrombocytopenic purpura (I.T.P.), the many abnormalities of coagulation involving all stages of coagulation were not suggestive of I.T.P. It was felt that the erythroid hyperplasia and absent iron indicated chronic gastrointestinal bleeding probably secondary to significant thrombocytopenia which developed 3 or 4 months previously and during which he had symptoms of a bleeding diathesis.

The extensive coagulation abnormalities with simultaneous depletion of fibrinogen, platelets, prothrombin, and Factors V and VIII suggest a consumption coagulopathy. Such a disorder has been described or suspected in an increasing number of clinical disorders including septicemia, giant hemangiomas, amniotic fluid embolization during placenta praevia, cardiac surgery with extracorporeal circulation, glomerulonephritis, malaria, and immune disorders.[1] *All of these disorders are believed* to initiate intravascular coagulation by release of thromboplastic substances or by activation of the intrinsic system through contact of Factor XII with altered endothelium or an artificial surface. Increased fibrinolysis usually accompanies a consumption coagulopathy and may even overshadow the deposition of fibrin. Abnormal fibrinolysis *may thus lead to incoagulability* of the blood and a diffuse hemorrhagic disorder. The accelerated fibrinolysis may further contribute to the inability of the blood to clot in the following manner. Recently several investigators have studied the properties of the breakdown products of fibrin released in the course of fibrinolysis during disseminated intravascular coagulation and have *found that certain* fibrin fragments or fibrin split products have anticoagulant properties.[1,4]

These several mechanisms involving intravascular coagulation, fibrinolysis, and fibrin split product formation produce a vicious cycle and severely deplete the blood of coagulation factors, particularly fibrinogen, platelets, and Factors V, VIII, and IX. This depletion is progressive and often associated with diffuse clinical bleeding. Bleeding from venipuncture sites and surgical wounds as well as spontaneous ecchymoses, purpura, or petechiae may occur.

Data now attest to the value of heparin in bleeding syndromes with evidence of consumption coagulopathy. The administration of intermittent intravenous doses of heparin apparently blocks the deposition of fibrin permitting the build up of adequate levels of fibrinogen, coagulation factors, and platelets. Fibrinolysis is usually



Fig 1 This roentgenogram made in August, 1966, shows fluid and thickened pleura in the right hemi thorax.



Fig 2 This roentgenogram made on March 23 1968, shows fluid in each pleural cavity with thickened pleura and atelectasis on the right.

meaningful indicator of a decreased left ventricular compliance The P wave con figuration in our patient s electrocardiogram is normal

Thus I conclude that this young man s respiratory difficulties were caused by chronic restrictive lung disease rather than by heart disease constrictive or otherwise

DR. HIBBS Review of this patient s chest films reveals rather long-standing pulmonary and cardiac pathology Chest x rays in October 1965 revealed marked right pleural thickening pulmonary congestion and cardiac enlargement with no apparent pleural effusion An A P standing spine film of the thoracolumbar vertebrae in July 1966 (Fig 1) revealed similar findings with right pleural effusion also present. Scoliosis was noted but considered minimal Chest films in late March 1968 showed bilateral free-pleural fluid right pleural thickening atelectasis, and notching of the ribs in addition to the previous vertebral and cardiac findings (Fig 2) A postcardiac arrest portable chest x ray (Fig 3) revealed subcutaneous emphysema increasing infiltration and fluid on the left, and fluid and pleural reaction on the right. An endotracheal tube was in place.

DR. KNOSPE This 11 year-old boy had a 6 year history of chronic intrathoracic disease which began with empyema at age 6 Shortly thereafter he developed asthma and during 3 months prior to admission symptoms of pulmonary or cardiopulmonary insufficiency appeared At about the same time, a worsening of his pulmonary status occurred and he had a prolonged episode of profuse bleeding following a dental extraction This was accompanied by a decrease in prothrombin time a low platelet level and a prolonged bleeding time Although he had occasional spontaneous ecchymoses there was no overt bleeding until he entered Presbyterian St. Luke s Hospital for evaluation of his pulmonary disease as well as failure of normal growth and development. During the course in the hospital profuse and prolonged bleeding from venipuncture sites was noted and a hematology consultation was ordered A coagulation profile revealed the following abnormalities a reduced prothrombin time fibrinogen level and platelet count reduced Factors II V and VIII a borderline Factor VII a prolonged thrombin time a shortened euglobulin lysis time

These abnormalities suggested markedly

chest was free of adhesions. The right ventricle was markedly dilated. The right atrial endocardium was somewhat fibroelastotic. The parenchyma of the left lung ere firm reddish brown hemorrhagic and somewhat fibrous and atelectatic on palpation. The right lung was completely atelectatic small, and fibrous. Extensive areas of the base of the right lung were characterized by dense focally hemorrhagic, fibrous, connective tissue Small cystlike hemorrhagic blebs, thought to be hemangiomas, were noted on the base of the left lung Microscopic examination of these and numerous other tissues revealed multiple diffuse hemangiomas. The gastric mucosa was hemorrhagic and focal areas of hemorrhage were noted in the mucosa of both the large and small intestines. The spleen was enlarged and a Meckel s diverticulum was found

Microscopic studies showed that the epicardial lesions consisted of a vascular cellular tissue characterized by numerou small capillary like angiomatous channels and plump, moderately uniform endothelial cells (Fig 4) These cells contained pale-staining ill-defined eosinophilic cytoplasm and plump spherical or ovoid basophilic nuclei. Many of the vascular spaces were small and slitlike while others were somewhat dilated or sinusoidal in configuration Mitotic figures or cellular pleomorphism were not prominent (Fig 5) Similar hemangiomas were noted throughout much of the pulmonary tissue bilaterally in the epicardium involving the diaphrag n round the esophagus, and in the peripai cr tic tissue.

The lungs owed microscopic evidence of intra-alveolar hemorrhage and edema. The subepithelial basement membrane particularly of the larger bronchi, was prominent and thickened (Figs. 6 and 7) In addition, numerous areas throughout the pulmonary tissue were occupied by

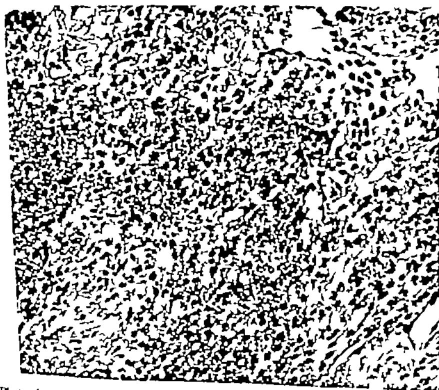


Fig 5 Photomicrograph of the smallest blood-filled capillaries of the angioma illustrated in Fig. 4. (Hematoxylin and eosin. ×135.)

reduced when the deposition of fibrin is inhibited and the anticoagulant effect of the fibrin split products is also removed[14]

This patient had classic clinical and laboratory manifestations of a consumption coagulopathy The cause of the coagulation disorder was not clear but it was suspected that chronic intrathoracic disease with chronic pleural or pulmonary infection may have in poorly understood ways initiated the disordered coagulation Further support for the validity of these concepts was improvement in the fibrinogen level following heparin administration The severe bleeding which followed bronchoscopy indicates that the therapeutic efforts were only partly successful and that the intratracheal bleeding was a critical factor in development of hypoxemia and a final ventricular arrhythmia which was the direct cause of death

DR LEE This 11 year-old boy was free of abnormalities at birth Subsequently at the age of 7 he began to have episodes of asthma and developed a right empyema following pneumonia During the last 4 years of his life he was able to attend school but did not thrive About 3 months prior to his death a tooth extraction was followed by constant hemorrhage for a 2 to 3 day period A marked thrombocytopenia was later demonstrated He was diagnosed as having a consumption coagulopathy and asthma. It was thought that the right lung might be a site of platelet sequestration and breakdown His condition was somewhat stabilized following hospitalization and consideration was given to pleural stripping or pneumonectomy in an attempt to correct the coagulation defect. Bronchoscopy was undertaken and this procedure was accompanied by cardiac arrest. The patient was successfully resuscitated but died several hours later

Autopsy revealed some subcutaneous emphysema in the anterior aspect of the neck a flattened right hemithorax a normal left hemithorax and extensive fibrosis involving the right pleural cavity pericardium and pulmonary tissues. The left



Fig 4 Photomicrograph of large and small vascular channels in the angiomatous tissue of the epicardium. (Hematoxylin and eosin. ×53.)

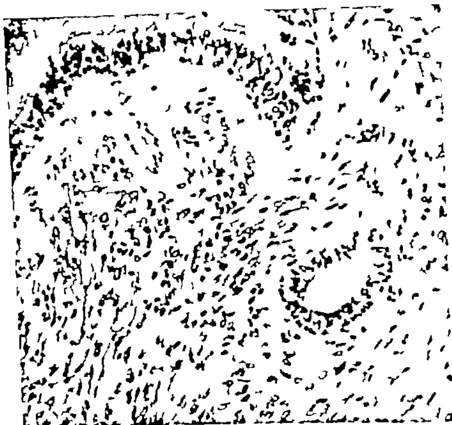


Fig. 7 Photomicrograph of a field of Fig. 6 to show the thickened hyaline subepithelial basement membrane and the infiltration of the bronchial wall by diffuse capillary hemangioma. (Hematoxylin and eosin. ×135.)

the mechanical situation whereby substantial platelet breakdown might occur resulting in thrombocytopenia. The cor pulmonale was probably secondary to prolonged pulmonary disease. The diffuse congenital angiomas, the marked impairment in respiratory function secondary to them, and the subsequent thrombocytopenia were all contributory to the patient's final illness and death.

DR. KNOARE. The finding of multiple hemangiomas was unexpected. Whether the hemangiomas preceded the episode of empyema at age 6 and their growth was stimulated by the infection or whether they developed after the episode of empyema must remain speculative.

The association of clinical bleeding and thrombocytopenia and multiple hemangiomas has been given an eponym, the Kasabach Merritt syndrome, after the original description in 1940. Since that time, about 73 ... been described in literature.[4-7] Various therapies, including radiation of the hemangiomas, splenectomy, surgical excision, pressure bandages, and corticosteroids, have been used in the treatment of this disorder. No therapy has been free of hazard or failure although improvement in the hemorrhagic diathesis has often followed their use.[8]

Many of these cases have a consumption coagulopathy with characteristic widespread depletion of coagulation factors. Furthermore following anticoagulant therapy such as the use of heparin, a repletion of coagulation factors has occurred lending further credence to the presence of a consumption coagulopathy. Histologic examination of the hemangiomas has demonstrated at times thrombi composed of masses of platelets enmeshed in fibrin.[9,10] Several factors may be involved in the initiation of the abnormal coagulation within the tumors. The vessels are tortuous, ...oring stasis of blood flow through the



Fig 6 Photomicrograph of wall of a bronchus with a thick hyaline subepithelial basement membrane and widespread angiomatous replacement of bronchial and pulmonary alveolar structure. (Hematoxylin and eosin. X 53)

angiomatous lesions similar to those described on the epicardial surface (Fig 8) In some areas these vascular structures were composed of thinwalled greatly dilated sinusoidal or cavernous structures occupied by large numbers of red blood cells. Slender fibrous walls occupied by fibroblasts and flattened endothelial cells separated the cystic spaces. In other areas, the vascular lumina were much smaller and the spaces separated by thicker fibrous walls. These lesions were accompanied by a few infiltrates of chronic inflammatory cells particularly small lymphocytes. Some vascular spaces were quite narrow with a slitlike configuration Areas which were more extensively involved with the vascular lesions revealed considerable fibrosis and fatty infiltration The tissue throughout was characterized by perivascular hemorrhage surrounding pulmonary blood vessels. In some situations the vascular lesion was present only in small microscopic foci frequently closely associated with bronchial structures. Here the endothelial and stromal nuclei were very plump basophilic and prominent. In contrast the vascular spaces were extremely narrow in these areas. In addition to close epicardial involvement with the myocardium the vascular lesion was also in close association with muscle of the diaphragm These lesions appeared to represent benign diffuse congenital hemangiomas which may or may not have undergone some proliferation later in the patient's life. The histologic appearance of these lesions was quite uniform throughout.

Frequently patients with diffuse congenital angiomas will have normal development for a time with clinical disease developing later in life. No vascular lesions were apparent at the time of decortication in the present case The lesions in this patient compromised respiratory function are probably the cause of the asthma reported and complicated the patient's course following infection thus providing

rence, and to some extent their size, appear to be of greater importance than their structural types. It is noteworthy that at times relatively small lesions only a few centimeters in diameter have been associated with thrombocytopenia. Histologic studies by Good and Kontras and associates[5] suggested the importance of intravascular coagulation. They described admixtures of platelets and fibrin in vascular spaces. Furthermore Gilon and Sheba reported platelet counts which were higher in blood recovered from the hemangioma than in the peripheral blood. McKay[1] wrote that stasis of blood within the tumor and traumatized or abnormal endothelial cells are important factors in this process. Multiple coagulation defects, as discussed by Dr Knospe, have been implicated and the disorder associated in the present case with diffuse angiomatosis may be regarded as a consumption coagulopathy from the hematologic point of view. Shim reported a mortality of 21 per cent in 74 accumulated cases. The gravity of this combination of pathologic entities has been once again demonstrated by the present case.

DR. AYER Were fibrin clots noted in the angiomas in the present case?

DR. HASS They were not conspicuous nor were there many platelet thrombi. This patient had been receiving heparin and the few fibrin clots may reflect a response to therapy. The vascular spaces in this case usually contained blood cells but not antemortem blood clots. Many spaces were empty.

DR. SCHILD Are the lesions in the present case to be regarded as benign or malignant?

DR. HASS There were rather uniform angiomatous lesions in which there was little mitotic activity or evidence of rapid growth. However a benign histologic appearance of angiomas does not preclude abnormal function in terms of platelet destruction or other activity eliminating coagulation factors. Furthermore the multiplicity of these tumors and their lack of demarcation add to complexity of interpretation. Diffuse angiomas probably represent mesenchymal dysplasias and usually are developmental defects. They may be localized or diffuse. The possibility of cellular proliferation or extension of the lesion even in those which are apparently benign should be recognized. The episodes of "asthma" in this case probably reflect impaired respiratory function secondary to the intrathoracic angiomas present since birth. The present case graphically illustrates the potential insidious or occult onset of abnormalities associated with inapparent congenital defects. The visceral angiomas in this case were unsuspected and invisible. Had there been visible easily recognizable angiomas they would have heightened awareness of the possible problems and facilitated therapeutic measures. Unfortunately a visible superficial subcutaneous hemangioma may ramify deeply and widely so that a surgical attempt at removal may lead to uncontrollable bleeding which is partly due to a complicating unsuspected consumption coagulopathy. Recently we had a case of this kind.

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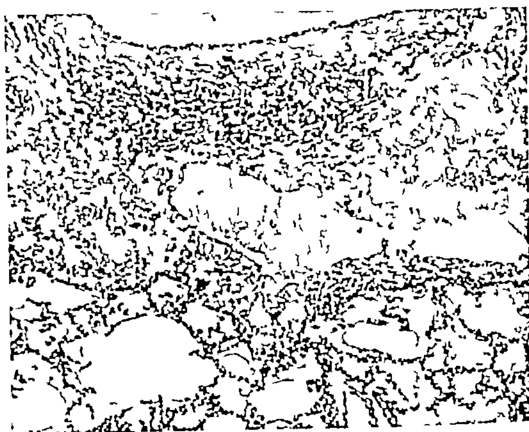


Fig 5 Photomicrograph of a medium-sized pulmonary artery with its adventitia and adjacent pulmonary alveolar structure largely replaced by the small and large vascular channels of the diffuse angioma. (Hematoxylin and eosin. ×100)

tumor Platelet agglutination may occur upon the abnormal endothelial lining of these vessels. This may be followed by fibrin deposition and the abnormal surface may initiate coagulation by activation of Hageman Factor (Factor XII) The abnormal vascular structures may also cause pathologic aggregation and sequestration of platelets[10,11] Depletion of coagulation factors may lead to a generalized hemorrhagic diathesis.

DR CLASEN The case just presented is quite interesting How frequent are such combinations of hemangiomas and thrombocytopenia?

DR LEE The combination of hemangiomata and thrombocytopenia is very uncommon However Shim[7] in a recent review stated that thrombocytopenia with hemangiomas may be more frequent in children and infants than is ordinarily thought. He reviewed the literature found 72 cases of hemangioma with associated thrombocytopenia and added two cases. Of these 36 were in the immediate newborn period although 4 older children 6 to 16 years of age were also included Tissue diagnoses were available in 43 cases. He alerted clinicians to the possible coexistence of these entities with the attendant potential hazards.

Hemangiomas with associated thrombocytopenia were first reported as Dr Knospe has noted by Kasabach and Merritt in 1940 Their case an infant 2 months old developed extensive purpura over much of the body The associated lesion involved much of the left thigh and buttock A case of pregnancy in an 18-year-old woman with giant hemangiomas, thrombocytopenia and fibrinogenopenia was reported about 2 years ago[18]

DR DAINAUSKAS Is the histologic type of hemangioma characteristic in this syndrome?

DR HASS The lesion reported by Kasabach and Merritt was a capillary hemangioma However a variety of histologic types of angiomas have been subsequently noted in this condition These include capillary as well as mixed forms, hemangioendotheliomas and hemangiosarcomas. Frequently the lesions are cavernous, single and extensive or multiple. Their occur

of renin secretion. The normal concentration of angiotensin in arterial blood in the dog and in man is probably in the region of 0.01 to 0.1 ng per milliliter (i.e. 10^{-11} to 10^{-10} Gm. per milliliter). The concentration which occurs in response to severe circulatory stimuli (such as hemorrhage) is probably in the range 0.1 to 1 ng per milliliter. In severe renal hypertension it may conceivably rise to much higher levels, but as a guide the "physiological" range is most likely to be 0.01 to 1 ng per milliliter. Unfortunately in many experiments in the intact animal the blood concentration is not measured, and only the dose is known. As a very rough guide, intravenous infusion rates of up to 100 ng per kilogram per minute might produce concentrations within this physiological range.

Effects on autonomic nervous system

Parasympathomimetic effects. Evidence of this action of angiotensin has come from studies of the response of intestinal smooth muscle which has a rich parasympathetic innervation by cholinergic fibers. When such tissues (e.g. guinea pig or rabbit ileum)[1,2] are exposed to angiotensin in an organ bath a contraction results which is increased by anticholinesterase and reduced by atropine or by botulinus toxin (which interferes with the synthesis and release of acetylcholine). Such results suggest that part of the effect of angiotensin on such tissues is mediated by cholinergic nerve endings in the tissue. This concept was supported by the experiments of Panisset[4] who studied the release of an acetylcholine-like substance into the organ bath when the tissue was stimulated via its nerve supply. In the presence of angiotensin (0.01 to 0.1 ng per milliliter) stimulation of the nerve caused an increased release of acetylcholine. Since intestinal smooth muscle contains both pre- and postganglionic fibers as well as parasympathetic ganglia this effect of angiotensin could be due to activation either of postganglionic cholinergic fibers or of preganglionic nerve terminals, or of the ganglia themselves. Angiotensin has not been found to potentiate the effects of cholinergic nerve stimulation in tissues where there are no ganglia so that the most likely interpretation of these results is that angiotensin can activate parasympathetic ganglia.

Activation of sympathetic ganglia. Presumptive evidence of this effect was first provided by Lewis and Reit[4] who demonstrated that intra-arterial injection of angiotensin close to the superior cervical ganglion of the cat caused contraction of the nictitating membrane whereas similar injections to the membrane did not. The smallest effective dose was 100 ng (by sudden injection) and the peak concentration was probably in the region of 100 ng per milliliter. Panisset[4] studied the release of an acetylcholine-like substance into the effluent from the perfused superior cervical ganglion of the cat and found that angiotensin in a concentration of about 0.5 ng per milliliter increased the amount of acetylcholine released in response to electrical stimulation of the preganglionic nerve. It is of interest that the effect of angiotensin on ganglionic transmission is not blocked by hexamethonium or pempidine[5,6] (see below).

Release of catecholamines from the adrenal medulla. Since the medulla is innervated by cholinergic preganglionic nerves and is in some respects the analogue of a ganglion it might be expected that angiotensin would facilitate the release of catecholamines; such an effect has been described in several species. Feldberg and Lewis[7] injected angiotensin into the aorta of eviscerated cats, assaying the released catecholamines by the response of the denervated nictitating membrane of the same animal; the smallest effective dose of angiotensin was 1 ng and no effect was found after removal of the adrenal gland. Robinson perfused the isolated cat's adrenal with an artificial perfusion fluid and measured the concentration of catecholamines in the venous effluent. Convincing increases of secretion were produced by injection of 0.1 ng and some increase was seen with doses of 0.01 ng or less; since the rate of perfusion was 0.5 to 5 ml. per minute it seems likely that concentrations as low as 0.01 ng per milliliter were effective.

Sustained increases of catecholamine secretion in response to infusions of angiotensin in the dog were reported by Peach and associates who infused angiotensin

Fundamentals of clinical cardiology

Effects of angiotensin on the autonomic nervous system

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The physiological role and mechanism of action of angiotensin continue to excite the interest of a large number of workers. Angiotensin has at least three different effects it causes contraction of a variety of smooth muscles, especially of vascular origin it increases the rate of secretion of aldosterone in a wide range of animal species It has effects at various sites of the autonomic nervous system

The first of these actions to be described was the effect as a direct vasoconstrictor which occupied the attention of cardiovascular investigation until the late 1950 s. Since then its two other types of action have excited renewed interest among research workers but the results in the two fields of work provide an interesting contrast. The autonomic effects of angiotensin are complex and their physiological role is still obscure, whereas the effect on aldosterone secretion is well defined and appears to be of physiological importance in the control of blood volume.

The first firm evidence that angiotensin could activate the autonomic nervous system in the intact animal was provided by the experiments of Renson and associates[1] who in 1959 demonstrated that angiotensin could cause contraction of the nictitating membrane in cats (whose nerve supply is exclusively adrenergic) this action was blocked by the alpha-adrenergic blocking agent, phenoxybenzamine. Since then a great deal of work has been done in this field and it is therefore somewhat surprising that no clear picture has emerged as to the physiological role of these effects, i e. what part they might play in the response to angiotensin generated in the blood stream by endogenous renin Nevertheless, these effects are interesting and it is worth discussing them in some detail to illustrate how extremely complex the effect of angiotensin can be The references cited are not necessarily the earliest ones, but have been selected as important ones which also give further references to much of the earlier literature

The effects which have been so far described fall into the following groups (1) parasympathomimetic effects and potentiation of the effects of cholinergic nervous activity (2) activation of sympathetic ganglia (3) stimulation of catecholamine secretion from the adrenal medulla (4) potentiation of the effects of adrenergic nerve stimulation (5) sympathomimetic effects due to an action on the brain and (6) inhibition of parasympathetic nerves to the heart by an effect on the brain

In considering the possible physiological role of such effects, it is most important to bear in mind the concentration of angiotensin necessary to produce these effects and to compare this with those known to occur spontaneously in response to changes

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due to the sympathetic nervous system because it is reduced by the adrenergic blocking drugs, phenoxybenzamine and propranolol.[23] A possible alternative explanation of this result is that adrenergic pathways in the brain were activated by angiotensin and further evidence is required before it can be concluded that angiotensin can activate the sympathetic nervous system by an action on the brain in physiological concentrations in the intact animal.

Inhibition of parasympathetic nerves to the heart due to an action on the brain. This effect can be demonstrated by infusions of angiotensin into the vertebral artery of the dog, which produces a rise of blood pressure due to an increase of cardiac output, which is unaffected by adrenergic blocking agents, but is almost abolished by atropine or vagotomy.[26] Such effects can be demonstrated at local concentration of angiotensin in the region of 0.02 to 1 ng. per milliliter.

Interaction of angiotensin with the sympathetic nervous system—site of action unknown. The preceding sections deal with the known sites of action of angiotensin on the autonomic nervous system, but there are a number of experiments which demonstrate a sympathomimetic action in which the site of action is unknown. It may subsequently transpire that the effects described fall into one or other of the categories already discussed, but until this has been shown they must be classified separately.

The first evidence of such an action has already been mentioned, showing an effect on the nictitating membrane of cats. A similar effect on vascular smooth muscle was demonstrated by Laverty,[22] intravenous injection of angiotensin (doses of 1,000 ng. upward) caused a rise of resistance in the isolated perfused hind limb of the rat which communicated with the body only by the nerves. The peak concentrations of angiotensin were probably over 100 ng. per milliliter.

Effects on the peripheral resistance have been demonstrated at lower concentration by McGiff and Fasy[29] and by Scroop and Whelan.[30] McGiff and Fasy injected angiotensin (100 ng. per kilogram) intravenously in the anesthetized dog and recorded renal vasoconstriction which was abolished by guanethidine, bretylium, or renal denervation but not by the ganglion blocking agent hexamethonium. The peak blood concentration in these experiments was probably about 3 ng. per milliliter. It is important to realize that the failure of hexamethonium to block this effect cannot be taken as evidence that the site of action of angiotensin was not on the sympathetic ganglia (see above). Scroop and Whelan infused angiotensin intravenously in man (dose 1,000 ng. per minute) and observed that the vasoconstrictor effect on the hand was greatly reduced by phenoxybenzamine or bretylium and did not occur in the sympathectomized limb or after denervation. The blood concentration of angiotensin in these experiments was probably in the region of 0.3 ng. per milliliter.

Effects on the heart have been described by several workers. Farr and Grupp[31] injected angiotensin (1,000 ng. per kilogram) intravenously in dogs, and noted a biphasic response of heart rate with a delayed rise above the control rate after the initial bradycardia; this delayed rise was accompanied by an increase of contractile force and was reduced by pronethalol or reserpine or by section of all nerves to the heart. It was not altered by adrenalectomy or by pentolinium or hexamethonium. Therefore, it cannot have been due to release of catecholamines from the adrenal medulla, but could have been due to an effect on ganglia (see above). The peak blood concentration was probably about 30 ng. per milliliter. Nubith and associates[32] and Kramey and co-workers[33] studied the effect on heart rate of rather low concentrations of angiotensin and concluded that there was activation of sympathetic nerves to the heart, but in their experiments interpretation is complicated by the fact that they stabilized arterial pressure during an angiotensin infusion and the effects on heart rate include the effects of controlled bleeding. Both groups of workers also studied the effects of angiotensin on heart rate after denervation of sinoaortic baroceptors (to prevent the reflex bradycardia in response to arterial hypertension) and they found a tachycardia. This was prevented by sympathetic blockade but not by ganglionic

intravenously in doses of 25 50 and 100 ng per kilogram per minute The two higher doses caused a significant increase of catecholamine concentration in the inferior vena cava

Potentiation of the effects of adrenergic post ganglionic nerve stimulation The first evidence of this effect of angiotensin was produced by Benelli and co-workers[10] who demonstrated that the isolated guinea pig vas deferens (which is innervated only by adrenergic nerves) responded more strongly to stimulation of the hypogastric nerves when angiotensin was present in the organ bath although angiotensin alone did not cause contraction These results were not confirmed by Hughes[11] who stimulated the vas deferens transmurally he suggested that the results of the Benelli group were due to the known effects of angiotensin at sympathetic ganglia which may have been present distal to the site of stimulation of the hypogastric nerve

Zimmerman and Gomez[12] also reported an effect which seemed likely to be due to some local interaction between sympathetic nerves and angiotensin In the perfused paw of the dog angiotensin infusion at 1 000 ng per minute increased the constrictor effect of sympathetic nerve stimulation the concentration of angiotensin was approximately 30 ng per milliliter Similar effects were seen in the dog kidney with concentrations nearer 1 ng per milliliter It is possible that these effects were due to the known effects of angiotensin on sympathetic ganglia because it is difficult to be certain that there were no ganglionic synapses distal to the site of stimulation of the nerve.

An alternative approach to this problem is a pharmacological one mimicking the effects of adrenergic nerve stimulation by the use of tyramine which is believed to act by releasing noradrenaline from sympathetic nerve terminals. This drug has no known effects on ganglia so that potentiation of the effects of tyramine by angiotensin cannot be due to facilitation of ganglionic transmission Unfortunately experiments with tyramine have usually involved injections or infusions into the whole animal and it is possible that it might cause release of catecholamines from storage sites in the brain rather than from peripheral ones. In spite of these reservations it is nevertheless interesting that chronic renal hypertension[13,14] or acute infusions of angiotensin at 30 ng per kilogram per minute to the dog[15] or at 50 ng per kilogram per minute into the rat,[16] cause an increase in the pressor response to tyramine but not to noradrenaline. These results suggest that angiotensin may interact with factors causing release of noradrenaline at sympathetic nerve terminals to produce an increased response of the target organ There is not yet sufficient evidence to be certain what is the nature of this interaction

Sympathomimetic effects due to an action on the brain The first convincing experiments showing that angiotensin could produce such effects were those of Bickerton and Buckley[17] who injected angiotensin into the arterial supply to the head of a dog which was crossperfused from a donor The only effective connection between the recipient's head and body was via the nervous system yet injection of angiotensin to the head caused a pressor response in the body which could be greatly reduced by an alpha adrenergic blocking agent. The blood concentration producing these effects was probably above 100 ng per milliliter

Attempts to demonstrate this effect with more physiological concentrations have not been very successful Infusions of angiotensin into the carotid arteries of the intact animal do not apparently activate the sympathetic nervous system Infusions into the vertebral artery of the rabbit[18,19] and the dog[20] do have a specific pressor effect but it has not been shown that this is due to activation of the sympathetic nervous system In the dog it is apparently due to inhibition of parasympathetic nerves to the heart, and a sympathomimetic effect can be demonstrated only in the vagotomized animal[20]

Another method of demonstrating an effect of angiotensin on the brain is to inject or infuse it into the cerebrospinal fluid but this is a very unphysiological route of administration and the concentrations required to demonstrate an effect are in the region of 100 ng per milliliter The resulting pressor effect seems likely to be

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blockade or preganglionic neurectomy These sympathomimetic effects could have been due either to a ganglionic or to a postganglionic action of angiotensin

Physiological role of effects on the autonomic nervous system In many of the experiments described above both the absolute concentration of angiotensin and the shape of the concentration line curve were very different from the physiological range. The question of the physiological concentration has already been discussed and a fairly broad range was accepted (0 0 to 1 ng per milliliter) but it is also relevant to consider the way in which the physiological concentration changes with time because endogenous changes of angiotensin are relatively slow whereas injections produce a very sharp rise and decline Infusions of angiotensin will mimic the effects of endogenous generation much better than will injections. Nevertheless in spite of reservations as to the physiological relevance of some experiments, there is a sufficient body of evidence to suggest that generation of angiotensin in response to endogenous renin secretion might affect the autonomic nervous system in nearly all the ways which have been described

The fact that these autonomic effects can be expected to occur in many physiological circumstances does not enable us to draw any conclusions as to their relative importance compared to the direct vasoconstrictor effects. The net effect on arterial pressure must be the complex resultant of many conflicting mechanisms. In response to the direct vasoconstrictor effect the primary rise of blood pressure would be antagonized by baroceptor reflexes and perhaps by facilitation of transmission at parasympathetic ganglia supplying the heart. It would be enhanced by any central action of angiotensin on the brain the adrenal medulla the sympathetic ganglia and the postganglionic sympathetic neurone. It is perhaps not surprising that no one has yet quantitated the relative importance of the various autonomic effects of angiotensin even in acute experiments and the problem becomes even more complex in chronic experiments. It remains at least a possibility that the major cause of the sustained rise of arterial pressure in chronic renal hypertension is due to the effects of angiotensin on the autonomic nervous system

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high operative mortality as well as a high failure rate in the surviving patients. Direct endarterectomy performed by incising the diseased vessel and enlarging it with a patch-graft of pericardium was extensively studied at the Cleveland Clinic, operating upon more than 200 patients. Unfortunately the operative mortality rate for procedures upon the left coronary artery remained over 50 per cent so the operation was finally abandoned remaining applicable only for short segments of the right coronary artery. With the high mortality rate from previous operative procedures, and the knowledge that the atherosclerotic process was usually diffuse and extended down into vessels only 1 to 3 mm in diameter there was a natural reluctance to attempt arterial anastomoses to such small tributaries, especially in patients with advanced coronary artery disease in whom any surgical procedure has a significant operative risk.

A final useful concept, gradually developed similar to that used with atherosclerotic disease in the lower extremities, is employing a long graft to bypass completely the atherosclerotic vessel. As stated earlier for the right coronary artery this often means a graft from the aorta to the origin of the posterior descending coronary artery on the posterior surface of the heart. Only by cautious clinical experience has it been demonstrated that such anastomoses can be consistently performed to the posterior surface of the heart, at first considered a difficult or perhaps impossible technique. The applicability of similar techniques to the circumflex coronary artery is now being widely studied. The anterior descending coronary artery however is much less accessible to bypass grafting because of its small size and the fact that near the apex of the heart it is often concealed in epicardial fat or myocardium. For these reasons, Green has frequently employed the dissecting microscope for operations upon this vessel.

Operative procedure

Cardiopulmonary bypass is usually employed, making it possible to stop the heart by occluding the aorta or by killing it by induction of ventricular fibrillation. Occasionally Favaloro has made preparations for cardiopulmonary bypass but has been able to complete the operative procedures on the right coronary artery without starting extracorporeal circulation. For operations upon the left coronary artery however extracorporeal circulation is mandatory. The oxygen requirement of the heart can be decreased by lowering the temperature to 30 to 32° C., at which temperature aortic occlusion for 10 to 15 minutes alternating with 4 to 5 minutes of perfusion, is well tolerated. An alternate technique with cardiopulmonary bypass functioning is inducing ventricular fibrillation which will still the heart although coronary perfusion continues.

Once bypass is established the patent distal arterial segment must be identified for anastomosis. Preoperative angiography is crucial in this regard making it possible to identify this segment without extensive operative dissection. One of the most serious technical hazards with operation is the risk of bleeding from epicardial surfaces following prolonged dissection to find the patent distal arterial segment. Usually on the right coronary artery the apex of the heart is tilted upward and the area of origin of the posterior descending coronary artery mobilized posteriorly at the interventricular groove. A bypass graft inserted at this point will supply blood directly to the left ventricle, through either the posterior descending coronary artery or the circumflex coronary artery varying with the anatomy of the coronary arterial circulation. This use of a long bypass graft from the aorta to the posterior descending coronary artery has greatly enhanced the applicability safety and effectiveness of bypass grafting in the right coronary circulation. The procedure is surprisingly analogous, on a miniature scale, to operative procedures for occlusive disease of the abdominal aorta in which bypass grafts are inserted from the aorta distal to the renal arteries to the femoral arteries in the thigh opposite the origin of the profunda femoral arteries.

With the anterior descending coronary artery anastomoses are usually performed within two inches of the apex of the left [illegible] circumflex

Venous bypass grafts for occlusive disease of the coronary arteries

Frank C. Spencer, M.D.
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One of the most exciting and surprising recent developments in the surgical treatment of occlusive disease of the coronary arteries is the initial good results obtained with saphenous vein bypass grafts. In a companion article in this series, Dr. George Green[1] has described early experiences with the use of the internal mammary artery for bypass grafting employing a dissecting microscope; this concept originated with Green and was developed in the laboratories at New York University.

The saphenous vein for bypass grafting in the coronary circulation was first widely used by Favaloro[2] at the Cleveland Clinic to bypass short segments of occlusive disease in the right coronary artery. Initially the grafts were interposed in the coronary artery, dividing the artery proximal and distal to the occluded segment. With experience increasingly longer segments of the right coronary artery were bypassed; it is now one of the most frequently performed procedures to bypass almost all of the right coronary artery, attaching the vein graft proximally to the aorta and distally to either the posterior descending coronary artery or the right coronary artery on the posterior surface of the heart near the interventricular groove.[3] The surprising feature of the bypass technique with published data only now becoming available[4] is that it seems applicable to large numbers of patients with coronary artery disease and can be accomplished with an operative mortality rate near 10 per cent—and probably with an even lower mortality rate with increasing experience.

Background data

Following the studies of Jacobson[5] several years ago which emphasized the value of microsurgical techniques with small arteries, a number of investigators[6] demonstrated the feasibility of vascular anastomoses to coronary arteries 2 to 4 mm. in diameter, thus establishing a sound basis for the operative technique currently employed. A pertinent question then is why has the feasibility of bypass grafting only suddenly been discovered?

For several years the widespread diffuse nature of coronary atherosclerosis has been repeatedly demonstrated by coronary angiography and postmortem examination. The initial hope that short segments of occlusive disease near the origin of the coronary arteries from the aorta could be frequently found and surgically corrected has not been sustained. Such localized lesions probably occur in less than 5 per cent of patients with occlusive coronary disease. Operative attempts to remove extensive atherosclerotic plaques by endarterectomy have been consistently associated with a

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high operative mortality as well as a high failure rate in the surviving patients. Direct endarterectomy performed by incising the diseased vessel and enlarging it with a patch-graft of pericardium was extensively studied at the Cleveland Clinic, operating upon more than 200 patients. Unfortunately the operative mortality rate for procedures upon the left coronary artery remained over 50 per cent so the operation was finally abandoned, remaining applicable only for short segments of the right coronary artery. With the high mortality rate from previous operative procedures, and the knowledge that the atherosclerotic process was usually diffuse and extended down into vessels only 1 to 3 mm. in diameter there was a natural reluctance to attempt arterial anastomoses to such small tributaries, especially in patients with advanced coronary artery disease in whom any surgical procedure has a significant operative risk.

A final useful concept gradually developed, similar to that used with atherosclerotic disease in the lower extremities, is employing a long graft to bypass completely the atherosclerotic vessel. As stated earlier for the right coronary artery this often means a graft from the aorta to the origin of the posterior descending coronary artery on the posterior surface of the heart. Only by cautious clinical experience has it been demonstrated that such anastomoses can be consistently performed to the posterior surface of the heart, at first considered a difficult or perhaps impossible technique. The applicability of similar techniques to the circumflex coronary artery is now being widely studied. The anterior descending coronary artery however is much less accessible to bypass grafting because of its small size and the fact that near the apex of the heart it is often concealed in epicardial fat or myocardium. For these reasons, Green has frequently employed the dissecting microscope for operations upon this vessel.

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With the anterior descending coronary artery anastomoses are usually performed within two inches of the apex of the left ventricle. Experiences with the circumflex

artery are too limited for comment at this time

A crucial question with operative technique is how small an artery can be successfully utilized for anastomosis. Most operative procedures reported by other investigators have been performed without magnification the anastomoses usually being to vessels with a diameter of 2 to 3 mm With the dissecting microscope Green has performed anastomoses to vessels in the range of 1 to 2 mm in diameter Certainly the dissecting microscope may greatly enhance the feasibility of bypass grafting, for a well recognized principle in the treatment of occlusive vascular disease is the disastrous results which quickly follow if an anastomosis is attempted to a vessel severely diseased with atherosclerosis. It is far better to choose a smaller more distal vessel in which atherosclerosis has not developed



Fig 1 Operative photograph showing a composite saphenous vein graft. The graft has been anastomosed proximally to the aorta as an end to-side anastomosis, and extends around the right border of the heart to connect with the right coronary artery near the origin of the posterior descending artery The graft is about six inches long A separate graft has been connected to this graft and anastomosed distally to the midportion of the anterior descending coronary artery On angiography at 6 months, the branch to the right coronary artery was occluded but the one to the anterior descending was patent. The patient remained in good condition.

The operative procedure may be complicated depending upon the number of anastomoses performed and the extent of dissection necessary Perfusion time with extracorporeal circulation may vary from one to three or more hours. If two anastomoses are performed one to a right coronary and one to a left coronary the vein graft is usually constructed by attaching a long segment of reversed saphenous vein between the aorta and the right coronary artery usually about six inches in length, and then inserting a second segment between the anterior descending coronary artery and the side of the previously inserted graft (Fig 1) An alternate technique is to attach both grafts directly to the aorta requiring an additional aortic anastomosis but providing some safeguard that operation would not be nullified if one of these anastomoses became stenosed.

The surprising result is that these patients seriously ill with advanced coronary artery disease have tolerated the long operative procedures well and usually maintain a satisfactory cardiac output following operation Arrhythmias have been the most frequent complication but myocardial infarction has occurred rarely Anticoagulants have not been employed afterward and most patients have been discharged from the hospital within two weeks after operation

Results

An impressive feature of the operative technique is that most patients have become free of angina almost immediately after completion of the operative procedure a striking contrast to the usual delayed response to arterial implants into the myocardium The mortality rate varies between 5 and 15 per cent. At New York University a total of 36 venous bypass grafts have been inserted Fourteen of these were single venous grafts, while in 8 patients venous bypass grafts to two vessels were employed In 14 other patients the internal mammary artery was anastomosed to the anterior descending coronary artery and the saphenous vein to the right coronary artery

Recently Johnson's group reported experiences with over 100 bypass venous

grafts in a series of 301 patients operated upon since February 1967 with an overall mortality rate of 12 per cent.[4] The severity of the coronary artery disease present in this group of patients is indicated by the fact that over one half had triple coronary disease with over 75 per cent stenosis in all three arteries, and one third of the patients had left ventricular failure. Double vein grafts were applied in 40 per cent of the patients. In the left coronary circulation a total of 61 grafts were inserted 7 to the circumflex coronary and 54 to the anterior descending. Forty-seven of these have been restudied by angiography finding 44 open and 3 occluded. In the right coronary circulation 58 patients with grafts have been restudied angiographically finding 52 patent grafts and 6 occluded. Angina has almost always been absent following operation. At present Johnson has not found cardiac failure of such severity that operation would be contraindicated.

Favaloro recently described his experiences with saphenous vein grafts, first used in May 1967. Two hundred twenty-two such operations had been performed by December 1968 including 15 anastomoses to the left coronary artery with two deaths and 207 to the right coronary artery with nine deaths. A few patients have been studied a year following operation finding a patent segment without any dilatation of the vein grafts.

In a recent personal discussion presented at the American College of Surgeons in October 1969 Favaloro stated that 322 saphenous vein grafts had been inserted into the right coronary artery and 61 into the left coronary.

Conclusion

It is apparent at this time with an operative experience less than two years in duration that bypass grafting is much more widely applicable to patients with coronary artery disease than previously thought, and can be performed with an operative risk near 10 per cent. Whether 10 to 20 per cent of patients, 30 to 40 or even more than 50 per cent of patients with occlusive disease will be found operable is not yet known. These questions depend upon the feasibility of arterial anastomoses to vessels in the range of 2 mm. in diameter and the increasing use of the operating microscope. It is significant that most of the data accumulated to date have been obtained without the use of magnification so, magnification may greatly extend the applicability of the operative procedure.

The serious question for the future is the long term patency of such small anastomoses. In the distal extremities, anastomoses to the dorsalis pedis artery may occlude in as high as 50 per cent of patients between one and two years after operation. Whether this will occur in the coronary arteries is not yet known. Nonetheless, striking rehabilitation of patients even for one year taking a very pessimistic view for long term patency will make the operation very worthwhile. Finally a major future question is the degree of protection provided such patients from myocardial infarction and the subsequent influence on longevity.

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Annotations

A new method for measurement of blood pressure in clinical shock

The measurement of blood pressure by the usually employed indirect methods in various circulatory shock states may sometimes be quite difficult and even inaccurate. This is due to the fact that the brachial artery pulsations and Korotkoff's sounds are greatly diminished in these conditions. Often there is a discrepancy in the blood pressure readings obtained by two different observers and sometimes no sounds may be heard at all in presence of significant blood pressure levels demonstrable by direct arterial cannulation. Comparison between auscultatory pressures in the arm and direct arterial readings taken with a needle inserted into the femoral artery frequently reveals that the direct femoral pressure is considerably higher than the pressure recorded in the arm by the auscultatory method.[1] Under these circumstances indirect auscultatory method may be grossly inaccurate so a direct method of blood pressure recording is required to follow these critically ill patients. By employing a slightly modified technique for the indirect measurement of blood pressure by auscultatory method we have often been able to get blood pressure readings in situations where no such measurements could be obtained by the use of the usual standard method. This is accomplished by inserting the diaphragm piece of the stethoscope under the lower edge of the blood pressure cuff over the brachial artery and then leaving it there during the subsequent rapid inflation and gradual deflation of the cuff.

By using the stethoscope in this position, the Korotkoff's sounds became clearer and more audible compared to the absent or muffled sounds that are heard in the same patients when the stethoscope is applied below the cuff in the antecubital space. In regard to the accuracy of these measurements, we recently had the opportunity to compare blood pressure readings obtained by this method with simultaneous direct measurements obtained through a needle into the brachial artery in two patients in shock in whom the Korotkoff's sounds were not heard at all by the use of standard auscultatory method. The direct systolic arterial pressure in both of these patients was 85 to 90 mm. Hg. The simultaneous blood pressure readings in opposite arm with the modified auscultatory method were within 5 mm. Hg of the direct arterial pressure measurements taken on multiple occasions. Furthermore, the blood pressure recorded in this way was always slightly less than the direct arterial pressures.

We are convinced that by this technique fairly reliable blood pressure recordings can be obtained without resort to arterial puncture in situations where the conventional method of taking blood pressure is not of much help. This technique, although no substitute for a direct arterial pressure measurement, should be employed in situations where the blood pressure is unobtainable by the standard methods and where an arterial puncture is not desirable.

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An interim visual display system for continuous monitoring of the ECG in coronary care units

Although it is now common practice to monitor the electrocardiogram (ECG) of patients with acute myocardial infarction on a continuous basis in order to detect transient rhythm disturbances, there has been no significant change in the physical format of the presentation of the ECG to assist monitoring personnel to perform their function better. The usual variety of rate meters, alarm units, and oscilloscopes now in widespread use was not engineered as a system

accuracy under the conditions of continuous monitoring. I the f ture, undoubtedly monitoring will be accomplished automatically by computers in the interim, it will continue to be done by nursing or other specially trained personnel. For the present w are causing the ECG to be displayed on a storage oscilloscope here the image is retained for several seconds, thus lessening the chance of overlooking solitary events and permitting more time for study of the ECG w form.

I practice, 5 inch storage display oscilloscope is used (Model 601 storage display unit, Tektronix, Inc Portland, Ore.). Each eep is incremented with stair step generator After an arbitrary number of steps the traces are automatically erased req iring 200 msec. I the event of an alarm or

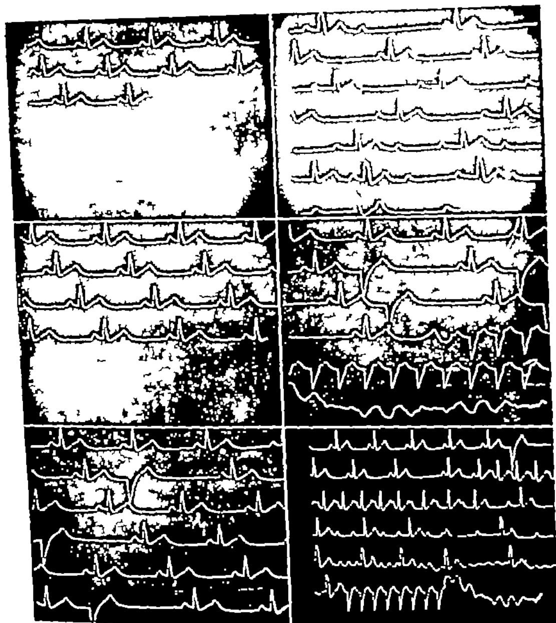


Fig. 1 *Left, top to bottom.* The oscilloscope sweep is incremented in series of steps so that the ECG is displayed from left-to-right and from top to bottom in continuous fashion before erasure and recycling.

Right, top. In the hold and nonstore mode, the previous ECG is held and the current ECG is displayed in conventional form. *Middle:* A ariety of arrhythmias is displayed. *Bottom.* Use of slower sweep speed permits storage of about 33 seconds of information before erasure.

manual hold an additional sweep is used at the bottom of the screen erase is inhibited and a Lissajous pattern is generated. This causes the beam to move too fast to be stored and permits the ECG to be displayed in a repetitive fashion to resemble the conventional trace.

The amount of ECG information to be displayed is a function of the sweep speed as well as the number of stair steps generated. Examples of rhythm disturbances are shown in Fig 1 They were simulated (Polyrhythm imulator Physio-Control Corp.) to show the ease by which rhythm distur bances can be detected and identified by using the system

The total cost of the entire display sy tem is l ttle more than that of the ordinary y tem. It is considerably less expensive than monitor ystems using video-scan techniques now becoming available The equipment can be mounted in standard relay-rack enclosures and may be adapted to any physical configuration desired. Since the torage oscilloscope has its own built in memory a memory unit is no longer essential Permanent records can be obtained easily and economically by using a camera adapted to the storage oscilloscope by the manufacturer (Model C 30P Tektronix, Inc.). It was used to obtain the photographs in Fig 1

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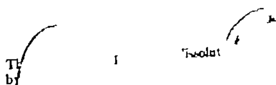
A thought about donor hearts

There must come a time when a donor heart in a recipient survives long enough so that every atom and every molecule of the heart are replaced by new ones through kinetic metabolic processes of the recipient and of the donor heart But are the ex changes in the donor heart program ied by the genes of the donor cell without nfluence from the recipient? Or are the progr mmings which re governed by the rec pient genes so different from those of the donor heart that once in the recipient and with the passage of sufficient time the donor heart is an entirely different one all tom and all molecules being new and organized differently more like that of the recipient? If different how different and how foreign with time to th t of the recipient? It may be possible for the kinetics of exchange among atoms and molecules to produc eventually a new and nonforeign organ for the recipient with the d nor heart as the base Perhaps w th a l ttle help, the new molecules and their patial interrelationships and interaction can be made to resemble the recipient sufficiently to be accepted forever

One can only recall the response of George Bernard Shaw to a critic wh accused h m of writing a bad play 20 years earlier Shaw replied that the man who wrote that play no longer existed It wa a different George Bernard Shaw who had written that play for hi physiologist friends had told him that ll atom and molecules of man are completely t rned er every 14 years.

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Streptokinase therapy in acute major pulmonary embolism*



perimental thromb nd p l onary emboli[a] in animals, in experiment l thrombi in man, and in patient with acute venou and arterial thromboembolic disease[4] Of the enzymes estig ted nly the two plasminogen acti ators, treptokinase

and urokinase, has proved acceptable as thrombolytic agents for clinical use.[13] Streptokinase is now readily available in a highly purified form but has the disadvantage of being antigenic in man. Pyrogenicity, a major difficulty with early preparations,[26,27] is no longer a significant problem provided that prophylactic corticosteroids are used. Urokinase is of human origin, not antigenic to man, and initial clinical investigations suggest that it produces a predictable dose response effect in most patients. The extraction and purification of this enzyme in a form acceptable for human use has proved difficult, and although this has now been achieved, the drug is still very expensive and relatively unavailable. Clinical studies with urokinase are currently in progress in the United States but by comparison with streptokinase, experience in the use of urokinase in man is limited.

The problems of the antigenicity of streptokinase are manifest in two ways. The first is due to the fact that streptococcal antibodies react with streptokinase. These antibodies, the result of previous streptococcal infections, are present in most patients and have to be neutralized before thrombolysis can be induced. The neutralizing dose of streptokinase cannot be predicted with any certainty because the concentration of streptokinase antibodies varies over a wide range from patient to patient. For this reason it is commonly recommended that a resistance test be performed and the dose of streptokinase be individualized for each patient. The second problem arising from the antigenicity of streptokinase is that treatment is followed by a marked increase in the levels of streptokinase antibodies, and this precludes further therapy should this be necessary over the next one to six months.

The use of streptokinase has been limited in the past by the need to perform streptokinase resistance tests on patients before commencing treatment. Although these tests are relatively simple, it may not always be convenient to perform them before starting treatment. In recent years attempts have been made to overcome this problem by introducing various standard dosage schedules. With this approach it is inevitable that some patients will receive an inducing dose in excess of their resistance and others a dose which fails to neutralize their streptokinase antibodies. High inducing doses in excess of the patient's resistance have been shown to be safe and effective; they produce rapid activation and depletion of plasminogen and give rise to a hemostatic defect which, however, is transient and asymptomatic provided that the circulating plasminogen is maintained at a low level by an adequate sustaining dose. On the other hand, inducing doses which fail to neutralize the circulating antibodies are pharmacologically ineffective. Therefore, to be of practical value, an arbitrary inducing dose should be sufficiently large to overcome the streptokinase resistance in a very large percentage of the population. This dose will be strongly influenced by the range and distribution of streptokinase resistance in the particular community in question. Verstraete and associates demonstrated that a standard dosage schedule was both effective and free of hemorrhagic complications. However the very high inducing dose of 1,250,000 U of streptokinase used by these investigators has the disadvantage that treatment in some patients becomes unnecessarily expensive. Other investigators when using a standard dosage regimen have used lower inducing doses, but the fibrinolytic effects of these lower dosage schedules has not been systematically evaluated.

Recently we investigated the safety and effectiveness of a standard dosage schedule of streptokinase (Streptase, Australian Hoechst Ltd.) in 50 randomly selected patients with thromboembolic disease. A streptokinase resistance test was performed on each patient who was then treated with a standard dose of 250,000 U of streptokinase infused over 30 minutes followed by 100,000 U per hour. The results of serial tests of fibrinolytic activity were then correlated with the streptokinase resistance in each patient, particular attention being directed to those patients with resistances in excess of the inducing dose. Forty-six of the 50 patients had a resistance of 250,000 U or lower and all of these patients developed an active thrombolytic state with rapid plasminogen depletion. The 4 patients with a streptokinase resistance in excess of 250,000 U showed a delayed fibrinolytic response, but, once obtained, the fibrinolytic effects were similar to those found in the other 46 patients. In general, the treatment was well tolerated; bleeding, the major complication, was usually restricted to oozing from sites of venepuncture but was severe in 2 patients.

These findings, together with other reports, indicate that it is possible to obtain a satisfactory fibrinolytic response with streptokinase in a large percentage of a community using a standard dosage schedule. The routine use of such a schedule would be acceptable only if a thrombolytic state could be achieved in a very high percentage of the community with a reasonably low inducing dose. On the other hand, if the distribution of streptokinase resistance in a community shows a very wide scatter with a significant proportion having a very high resistance, it would be far more economical to individualize treatment than to treat all patients with a very high inducing dose.

Theoretically, major pulmonary embolism is a particularly attractive indication for thrombolytic therapy. The embolus is usually composed of recent thrombus and the effects of therapy can be assessed objectively by angiographic, hemodynamic, and lung scanning studies. It has been shown that both streptokinase and urokinase accelerate resolution of pulmonary emboli in animals. More recently, angiographic improvement has been documented following thrombolytic therapy with streptokinase and urokinase in patients with severe pulmonary embolism. Despite these encouraging results the question as to whether or not the plasminogen activators accelerate dissolution of pulmonary embolism and improve immediate survival in man remains unanswered. Spontaneous resolution of major pulmonary embolism has been demonstrated in man by serial angiography but the speed with which resolution occurs is unknown. Recent investigations suggest that the majority of large

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Streptokinase therapy in acute major pulmonary embolism*

The feasibility of producing dissolution of thron bi by enzymatic means has been demonstrated in ex peri ent l thromb [a] and pulmonary emboli[2] in animal i experimental thrombi in man,[4] and in patie t with acute enous and arterial thrombo-embolic disease Of the enzymes investigated, only the two plasminogen activators, streptokinase

*This study was supported by grant from the National Heart Foundation of Australia.

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pulmonary emboli in otherwise healthy patients eventually undergo resolution in a matter of weeks, but that resolution is often delayed for many months in patients with underlying cardiac or respiratory disease.

In a recent study the clinical hemodynamic, and angiographic effects of streptokinase were investigated in 18 patients with major pulmonary embolism.[14] The diagnosis of major pulmonary embolism was confirmed by pulmonary angiography and the catheter was then left in the main pulmonary artery and used for the streptokinase infusion, for serial pulmonary artery pressure measurements and for further pulmonary angiograms. The loading dose of streptokinase was calculated from the resistance test but in 12 patients a standard loading dose of 250 000 U was infused over 30 minutes before the result of the resistance test was available Treatment was continued for at least 24 hours with a maintenance dose of 100 000 U per hour and the fibrinolytic and therapeutic effects were assessed by serial tests of fibrinolytic activity serial pulmonary artery pressure measurements, and by a second angiogram One patient was treated within 48 hours of abdominal surgery with a modified dosage schedule which was carefully monitored to produce only mild systemic fibrinolytic activity

Fourteen of the 18 patients improved clinically in the 24 hour period following the commencement of streptokinase therapy Of the 4 who failed to show initial improvement, 2 subsequently died and 2 required pulmonary embolectomy which was successfully performed in both The indications for embolectomy were cardiac arrest 3 hours after beginning streptokinase in one and recurrent pulmonary embolism 24 hours after beginning therapy in the other Autopsy in the other 2 cases showed severe pulmonary arterial obstruction by organized thromboembolism

Sixteen patients had angiograms repeated 24 hours after streptokinase therapy Eight showed marked improvement 3 moderate improvement 2 slight improvement, 1 had a recurrent embolus, and the 2 patients who died showed no significant change. In general the clinical, angiographic, and hemodynamic improvement was most marked in patients who were treated soon after a single episode of major pulmonary embolism and least marked in those who had evidence of progressive or persistent pulmonary embolic obstruction for more than 1 week. These findings are consistent with the experimental observations both in man[4] and in animals that venous thrombi become more resistant to therapeutic thrombolysis as they age.

The findings with streptokinase may be compared with observations made on 7 patients with major pulmonary embolism following 24 hours of treatment with continuous intravenous heparin[15] Three of these patients had recent acute embolic episodes and the other 4 had recurrent emboli with a recent major episode Five of the 7 patients (including the 3 with single acute episodes) showed no evidence of resolution, either hemodynamically or angiographically after 24 hours, and the other 2 showed only minimal resolution. Thus, although spontaneous resolution of major pulmonary embolism eventually takes place,[16] it is probable that significant resolution of 24 hours is uncommon.

Even if thrombolytic therapy does accelerate early resolution of major pulmonary embolism in man, it is unlikely that this form of treatment will ever have a strong influence on the overall mortality rate from pulmonary embolism. This is because the majority of patients who die from pulmonary embolism do so before any treatment can be instituted.[20,21] It is probable that a very significant number of these deaths would be prevented if anticoagulants were used prophylactically in high risk patients[22-25] and if clinically recognizable minor thromboembolic episodes were treated promptly with adequate doses of heparin.[26-28] Nevertheless, a significant proportion of patients who die with major pulmonary embolism do survive for 24 to 48 hours, and it is in this time period that thrombolytic therapy may fill an important role. While some of the delayed deaths may be caused by recurrence or propagation of the embolus, it is likely that many are caused by the direct hemodynamic consequences of the initial embolic obstruction. The survival rate in this group should be improved if rapid resolution of the embolus is achieved. Thrombolytic therapy may have an even more important place in patients with underlying cardiac or respiratory disease in whom spontaneous resolution is often delayed.[19] Resolution in these patients may not only improve the immediate mortality rate from acute pulmonary embolism but may decrease morbidity from the consequences of persistent embolic obstruction

In spite of the encouraging results obtained thus far the ultimate assessment of the role of thrombolytic therapy in the treatment of pulmonary embolism must await controlled clinical trials. One such trial with urokinase is currently in progress in the United States[29] and its outcome is awaited with interest. Whatever the result, major pulmonary embolism is likely to remain a common cause of death in hospital patients until more attention directed to prophylaxis in high-risk groups and to early and adequate heparin treatment of patient with minor thromboembolic episodes.

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Letters to the editor

Coronary surgery

To the Editor:

Dr. Irwin Ehrlich's thoughtful letter in the December 1969 issue of the AMERICAN HEART JOURNAL raises larger issues: In the development of *new methods of treatment* and the extension of old ones to new groups of patients, why are not the same standards demanded of the surgeon as of the medical cardiologist? Therapeutic review committees, journal editors and reviewers, and the F.D.A. demand careful design and control of drug *trials* before they may be published and the medicines licensed. Surgical procedures attain widespread application before anyone begins to question their obvious results (e.g., internal mammary ligation, glomectomy for asthma). Hemodynamic improvement and metabolic amelioration are worthy objectives, but not if gains to the patient cannot be objectively demonstrated. Portacaval shunt for prophylaxis of esophageal varices corrected the hemodynamics, but controlled studies showed its apparent worthlessness. The point is that procedures reported without properly matched and concurrent controls give us only numerators—worthless without corresponding denominators.

The work on coronary surgery has been brilliant technically and holds much promise for vast numbers of people. The surgeons and their cardiologist colleagues cannot be faulted on grounds of expertise and good intentions—they are superb physicians. The problem is the philosophic gap which permits acceptance as obvious the results of uncontrolled experience followed by a rush to apply and to publish. In any series, half the patients should be matched controls, *assigned by randomization,* so that chance alone will dictate which patients among those considered to qualify for a procedure will actually be operated upon. This could have helped settle the issue several years ago. Until this happens *we really do not have conclusive reasons for recommending* coronary surgery of any type. If patients who have undergone an operation fare less well or even equally well as matched control patients, that operation must be considered an assault on the patient.

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How to evaluate the S-T segment elevation during or after exercise

To the Editor:

The present, essential criterion of a positive two-step test is an S-T segment depression to some extent below the isoelectric level. Inversion of T waves and the reversal of previously negative T waves are not regarded as criteria of a positive test although such changes may be abnormal.

In our clinical experiences, when the exercise test was performed in patients after acute myocardial *infarction* in their rehabilitation stage, the most frequent changes by exercise were the appearance or increase in the S-T segment elevation in leads reflecting the infarcted area and the S-T segment depression in leads reflecting the noninfarcted area. The T wave change was an inversion or the reversion of a negative T wave to an upright position in leads reflecting both the infarcted and noninfarcted areas. These ST-T changes were more remarkable in patients shortly after the acute myocardial infarction, and less in patients with a longer rehabilitation period after the infarction.

In some patients with variant angina pectoris or a similar condition, the electrocardiogram during or after exercise showed the S-T segment elevation, and in some patients with angina pectoris it presented the transient normalization of previously depressed S-T segment to the base line. Accompanied T wave change was an inversion or the *reversion of a negative T wave to an upright position.*

How to evaluate these electrocardiographic changes during or after exercise has not been assessed at present in detail, although the appearance or *increase in S-T* segment elevation *of 1 mm.* or more, T wave inversion or the reversion of a negative T wave to an upright position was assumed as an abnormal response during exercise.

I wonder how Dr. Master evaluates the S-T segment elevation or the normalization of a previously depressed S-T segment to the base line as well as T-wave changes during or after exercise in ischemic heart diseases, in addition to his present criteria of a positive two-step test.

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Editorial

Electroconversion of cardiac dysrhythmias

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Electrical current across the myocardium may cause ventricular fibrillation but may also be used to terminate ventricular and atrial dysrhythmias. The rhythm disturbance we now call ventricular fibrillation was first described by Hoffa and Ludwig in 1850. Twenty-nine years later the first industrial accident involving electricity was reported in France, but the realization that electrocution when fatal usually resulted in ventricular fibrillation required many more years for general acceptance. A major step forward in actual treatment occurred with a report written almost as an afterthought in papers dealing with the effects of electrical current on the myocardium that a direct current shock across the heart would terminate ventricular fibrillation in dogs. This fact, however, continued generally unrecognized or seemed largely forgotten until the whole subject of electrical defibrillation was restudied by Kouwenhoven, Hooker and Langworthy[4] in a series of experiments over several decades. These workers were able to show that defibrillation of the ventricles could be achieved by passing a current of 1 amp at 130 volts for 0.1 sec across the hearts of well-oxygenated dogs and this was confirmed by Wiggers.[7] Eventually in 1947 the first successful human defibrillation was performed by Beck, Pritchard and Feil. Alternating current seemed preferred for defibrillation in this country, yet workers in Europe, particularly Gurvich and Yuniev[8,9] in the Soviet Union and Peleška[11,12] in Czechoslovakia reported extensively on the use of direct current and delineated the electrical characteristics needed to provide safe DC defibrillation. It is perhaps pertinent to consider briefly the electrical differences between alternating and direct current when used for defibrillation of the heart. Much of the confusion in the literature when considering the relative merits and demerits of each relates to the infinite number of wave forms obtainable following discharge of a capacitor as occurs using direct current; in contrast the alternating current wave form is constant and determined at the power station. The wave form and magnitude of a DC discharge varies with the design of the circuit and the important variables relating to its safe clinical use are the capacitance of the condenser, the value of the inductance of the circuit, the resistance between the patient electrodes, and the rise time of the waveform. Electrode paddles large enough to prevent high current density across areas of the myocardium are essential. An electrical circuit which produced an acceptable waveform was described by Lown and associates in which a capacitor of 16 microfarads (μf) is discharged across an inductance of 100 millihenrys (mh) and across the total body impedance. The mean duration of this wave form is about 2.5 msec., and after ringing is kept to a mini-

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Book reviews

ADVANCES IN MICROCIRCULATION. Edited by H. Harders, New York, 1969. S. Karger AG. 103 pages. Price $7.80.

This volume on advances in the microcirculation consists of six reports. The reports are concerned with studies of the respiratory distress syndrome of the newborn, microkymography, early microvascular reactions to slow and rapid thawing of frozen tissues, experimental hepatic venoocclusion disease, peripheral plasma layers in pulsatile flow in glass fibers, and blood rheology related to shock. These papers are all interesting and important. All investigators of the microcirculation and of peripheral vascular physiology will find this monograph extremely interesting. Unfortunately, more subjects were not included, but the six studies reported are important.

EXTRACORPOREAL CIRCULATION FOR OPEN HEART SURGERY. Pathophysiology, Apparatus, and Methods, Including the Special Techniques of Hypothermia and Hyperbaric Oxygenation. By E. Converse Peirce, II, M.D. Springfield, Ill., 1969. Charles C Thomas, Publisher. 117 pages. Price $9.50.

This short monograph is highly specialized. It should be of no value to the experienced practicing cardiac surgeon. It may be of service to those who are entering the field of open-heart surgery since the book is short and concerned with technique and methods. In less than 90 pages of text, the author discusses apparatus, pathophysiology, methods, hypothermia, and hyperbaric oxygenation, all complex aspects of open-cardiac surgery. Obviously, those who read this book must do so in conjunction with a detailed study of the medical literature.

EXPERIMENTAL METABOLIC CARDIOPATHIES AND THEIR RELATIONSHIP TO HUMAN HEART DISEASE. Annals of the New York Academy of Sciences, vol. 156, article 1. New York, 1969. 625 pages. Price $26.00.

This is a rather extensive presentation of the proceedings of the New York Academy of Sciences meeting on cardiomyopathies held in New York City during Jan. 9 to 11, 1967. This important problem of diseases of heart muscle was reviewed by a selected group of investigators engaged in a study of isolated aspects of cardiomyopathy. The conferences were divided into six parts concerned, respectively, with (1) ultrastructure of the normal and diseased myocardium, (2) cardiopathies and factors influencing myocardial degeneration, (3) genesis and prevention of cardiopathies, (4) cardiac pathology induced by isoproterenol and related amines, (5) progress in studies of cardiac hypertrophy, valvular lesions, and cardiac failure, and (6) primary cardiomyopathies and congestive heart failure in clinical medicine. Obviously, the entire subject of cardiomyopathies was not discussed. Nevertheless, this publication contains many interesting and important aspects of the many problems related to the cardiomyopathies. The weakest section was concerned with clinical aspects of the cardiomyopathies. This is unfortunate since the clinical problems are not only important and difficult to manage, but the disease is extremely common in many parts of the world. It is even fairly common in the United States and Europe. This publication should interest all cardiologists and investigators studying the myocardium.

HYPERLIPIDEMIA & HYPERLIPOPROTEINEMIA. By Shafeek S. Sanbar, M.D., Ph.D. Boston, 1969, Little, Brown & Company. 153 pages. Price $8.95.

Sanbar has summarized in about 150 pages the basic concepts related to hyperlipidemia and hyperlipoproteinemia. The presentation is clear and the essentials, as related to the practice of medicine, are made simple for those who are not actively engaged in research in this field. The five figures and tables are well selected. The five hyperlipoproteinemic types for man are well defined in a table on p. 142. A study of this book reveals the inadequacy of the present state of knowledge of the etiology and prevention of arteriosclerosis. Nevertheless, the physician and student must keep informed of developments and existing concepts and practices. Whether or not the recent interest in lipoproteins and diet control has influenced the incidence and severity of atherosclerosis is not known. The incidence of coronary heart disease continues to rise, however. Regardless, Sanbar's monograph is a good summary and is recommended to busy physicians and students.

of atrial or ventricular rhythm disturbances approaching 90 per cent is common.[37-43] Furthermore, DC shock will often succeed even when the dysrhythmia has been shown to be quite resistant to drugs administered to maximal tolerance.[44] Digitalis should be stopped for 24 to 48 hours before treatment which should be postponed in those patients with evidence of digitalis toxicity. The incidence of postconversion ventricular rhythm disturbance *is highest in this group*[[illegible]] and animal experimental work has confirmed the potential hazard of high-energy DC discharges in the presence of heavy digitalization.[[illegible]] Many workers precede electroconversion with quinidine.[[illegible]] Rosen and Lown[[illegible]] have reported that quinidine not only improves *the chances of remaining in sinus rhythm* after the shock but also diminishes the electrical energy needed to bring about sinus rhythm and reduces the incidence of postconversion rhythm disturbances; other workers,[[illegible]] however, have not found this to be so. Although general anesthesia is not mandatory,[[illegible]] a short-acting barbiturate is preferred,[[illegible]] particularly in the anxious patient or when more than one shock is needed. Elective treatment should always be undertaken under anticoagulant cover unless the risk of embolism or thrombosis is known to be negligible.[[illegible]] The shock may be administered across two anterior paddles or using an anterior and a posterior paddle. The latter *is more convenient as the patient* lies on the posterior paddle and, therefore, only one paddle need be grasped by the operator, an important safety measure particularly using apparatus in which one paddle is grounded. It has been reported that the anterior and posterior paddle position significantly lowered the energy required for electroconversion,[[illegible]] but others[[illegible]] could not confirm this. Using either paddle position, however, it is important that small energy levels are used first and if unavailing shocks are repeated at increasing energy level settings. For an adult an initial setting of 25 to 50 J would be satisfactory, increasing in 25 to 50 J steps, but if heavy digitalization is present, the initial shock should be 5 to 10 J. The initial setting for a child would be 5 *to 10* J delivered across appropriately sized pediatric paddles, *increasing* by 5 to 10 J steps. There should be considerable *reluctance to exceed an* energy level setting of 300 J in an adult being treated for a chronic rhythm disturbance *although the* situation may be entirely different when presented with an acute dysrhythmia which is producing serious hemodynamic effects. Repeated ventricular ectopic beats immediately after the shock should be terminated by an intravenous injection of 50 mg of lidocaine. The most common dysrhythmia to be treated has been atrial fibrillation for which a success rate of nearly 90 per *cent has been reported* in several large series involving many hundreds of patients.[[illegible]] Atrial flutter and tachycardia may be less successfully terminated,[[illegible]] but even so the average success rate is likely to exceed 80 per cent. Ventricular tachycardia has been a particularly rewarding *dysrhythmia to treat.*[[illegible]] *An important* factor on which success depends is the duration of the atrial dysrhythmia; the immediate success rate falls progressively to less than 50 per cent when atrial fibrillation has been present for five years or longer;[[illegible]] similarly, a cardiothoracic ratio of 50 per cent or *more* and *selective* enlargement of the left atrium lessen the chances of success.[[illegible]] Patients with idiopathic atrial fibrillation are exceptional, their success rate being the lowest of any group even in the absence of *these unfavorable signs.* Complications following cardioversion are *not as rare as initially* predicted and do not only relate to the drugs given to maintain sinus rhythm as suggested first.[[illegible]] In a recent paper[[illegible]] an incidence of complications of 14.5 per cent among 220 patients treated was reported, which included raised levels of the serum enzymes, pulmonary edema in *sinus rhythm,* electrocardiographic changes suggestive of myocardial infarction, and pulmonary or systemic emboli. An increased incidence of these complications could be correlated with higher energy level settings—at 150 J there was a 6 per cent incidence of complications, which increased to more than 30 *per cent at the* 400 J setting. The number of patients remaining in sinus rhythm after treatment has been disappointingly small. A 36 month follow-up involving some 183 patients[[illegible]] has reported that only 28 per cent remain in sinus rhythm, the majority who

mum (slightly overdamped circuit) DC defibrillators are calibrated in joules (watt seconds) and their energy output can be calculated from the formula

$$\text{Energy (J)} = \frac{\text{Capacitance}}{2} \times \text{Voltage}^2$$

Commercially available DC apparatus has a range which varies from <5 to 400 J but this of course reflects only the energy delivered to the skin and not across the heart For alternating current the electrical energy delivered will depend on time as well as resistance according to the formula

$$\text{Electrical energy (J)} = I^2 \times \text{Resistance} \times \text{Time}$$

where I = current in amperes This can be substituted to read

$$\text{Electrical energy (J)} = \frac{(\text{Voltage})^2 \times (\text{Time})}{\text{Resistance}}$$

and resistance can be shown to be greatest in the skin The essential electrical difference between AC and DC defibrillation is that although DC develops many times the power of AC it expends much less energy in doing so by virtue of its shorter duration (AC = 0 1 or 0 2 sec DC = 0 0025 to 0 004 sec) Furthermore the heat which is generated is less with DC current particularly if repeated shocks have to be used [17] and in addition depression of ventricular function which follows both AC and DC shocks is less with the latter [18] The effect of electrical energy on the myocardium depends on the current rather than the voltage[19] and this is true for both AC or DC [20] Currents developing less than 1 amp across the myocardium may well cause ventricular fibrillation Those exceeding 1 5 amp will stop fibrillation.[21] However only 10 to 30 per cent of the total electrical energy applied to the chest wall will pass across the myocardium[22] so that 50 to 400 J may be required for transthoracic defibrillation Despite much controversial evidence most workers now accept that DC is more effective than AC for ventricular defibrillation[20] although it should be stressed that the wave forms and duration of the current are so different as to make a true comparison impossible Up to 1960 electrical wave forms, either AC or DC were used only to terminate ventricular fibrillation the first AC termination of an organized dysrhythmia was that reported by Lown and his colleagues[23] in 1961 Other workers reported success using this method[24] although the experience of Zoll and Linenthal[25] had already demonstrated the potential hazards of AC in treating rhythm disturbances other than ventricular fibrillation There seemed little doubt therefore that AC while usable for terminating ventricular fibrillation could not be recommended for electively treating atrial rhythm disturbances or ventricular tachycardia

A transmyocardial DC shock will occasionally be followed by ventricular fibrillation For many years a vulnerable period had been postulated in a wide variety of animals[26-30] during which time the heart is particularly prone to ventricular fibrillation This period was shown to be 27 msec. before the end of systole in the dog [26] A similar period of atrial vulnerability was also demonstrated [27] The vulnerable period of the ventricle occurs just prior to the apex of the T wave at a time when nonuniform recovery from the refractory state is occurring [31 32] Re-entry of the depolarization wave occurs and self sustained activity favored Recently the studies of Castellanos and associates[33] have shown that a vulnerable period to fibrillation also occurs in the human heart. Most apparatus used to terminate rhythm disturbances by DC shock therefore incorporate a circuit which allows the discharge to be triggered by the R or S wave and so avoid this vulnerable phase other workers[34] deliberately use no synchronizer without dire consequences. The important parameter however when no synchronizer is used is to ensure that sufficient energy is delivered to allow a current of at least 1.5 amp across the heart smaller energies developing 0 5 to 1 amp may be dangerous in other words increased energy level settings are mandatory

Many thousands of patients have been treated by synchronized capacitor discharge following the initial report of its use by Lown and his co-workers,[35] who called the method cardioversion [36] Subsequent reports have completely justified the initial confidence in the technique and an over-all success rate for the termination

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revert do so by the end of the first month of successful electroconversion The highest incidence of reversion is within the first day nor does quinidine always help to maintain sinus rhythm [43] whether adminis tered as the standard quinidine prepara tion[41] or in a slow release compound whose dosage is controlled by quinidine blood levels [43] Patients in whom atrial fibrillation is of long duration that is more than three years or in whom significant underlying heart disease occurs or in whom radiographic enlargement of the heart is present[41] are particularly liable to revert to their previous dysrhythmia Once more patients with idiopathic atrial fibrillation are exceptional they do not remain in sinus rhythm even in the absence of these unfavorable circumstances.

Despite this there is no doubt that hemodynamic benefit may be achieved in sinus rhythm [44-46] particularly when patients are studied at progressive exercise loads[41] and certain groups of patients can only be maintained free of cardiac failure by re peated electrical termination of episodes of atrial fibrillation

Under favorable circumstances direct current shock is safer and more effective than quinidine and should be the first treatment in the management of serious acute dysrhythmias of whatever cause (but not digitalis-induced dysrhythmias) when energy level settings of 50 to 400 J may be used On the other hand patients with chronic dysrhythmias may require maxi mal energy settings to achieve sinus rhythm which they not infrequently main tain for a disappointingly short time Al though hemodynamic benefit may occur in sinus rhythm complications often follow electroconversion in this group and relate to the higher energy levels needed Each patient requires careful individual assessment to determine his chances of being brought into sinus rhythm and the length of time during which sinus rhythm is likely to be maintained Energy settings exceed ing 300 J can rarely be justified in this group and should be used with the knowl edge that complications are likely in 30 per cent of patients treated in this way

Many workers[46, 47] are now investigating other electrical wave forms and more recently newer methods allowing defibril lation using low-energy electrical current have been reported [44, 45] The method of terminating atrial tachycardia or flutter in which a timed electrical impulse is introduced into the cardiac cycle[44] is par ticularly exciting for it seems quite un necessary to treat an atrial rhythm disturbance by passing a high-energy current across the ventricular myocardium as at present.

While the introduction of synchronized capacitor discharge into clinical practice has been an exciting advance much more effort is needed for a better understanding of the basic mechanisms of dysrhythmias to allow a more physiologic approach to be developed for their treatment and for the maintenance of sinus rhythm

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Clinical communications

The contractile state of the hypertrophied left ventricular myocardium in aortic stenosis

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In past years it has become apparent that myocardial contractility is not readily assessed by standard hemodynamic measurements, such as cardiac output, left ventricular pressures, or stroke work.[1,2] Greater insight into the contractile state of the myocardium is provided when the velocity aspects of the ventricular contraction are taken into consideration. In this respect, investigations on the relationship between the velocity of contraction and tension have proved most helpful. This concept was first described in the isolated cat papillary muscle[3] and was then applied to the intact canine heart[4,5] and recently to the human left ventricle.[6-8] Gault and associates[6] have shown that during ejection at a comparable left ventricular peak tension the velocity of shortening of the contractile elements was definitely lower in patients with left ventricular myocardial disease than in a control group without myocardial dysfunction. While these findings might be expected because 7 out of 9 patients with myocardial disease had abnormal left ventricular dynamics at rest, there is considerably more controversy concerning the contractility of the heart hypertrophied by chronic pressure load. It would appear that many of the conflicting results stem from the differences in experimental procedures and measurements on which evaluation of the contractile function are based.[9-13] The most recent observations in papillary muscles from the hypertrophied right ventricle of cats and in the hypertrophied intact canine left ventricle,[14] where the assessment of the contractile state was carried out by measuring factors related to the velocity of muscular contraction, show under chronic pressure load a decreased myocardial contractility.

Using a similar approach Levine[7] has evaluated left ventricular contractility in 5 patients with aortic stenosis. The maximal velocity of shortening of the contractile elements, determined by extrapolation of the inverse portion of the tension velocity curves of auxotonic systoles, was clearly diminished in those 3 patients who pre

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The contractile state of the hypertrophied left ventricular myocardium in aortic stenosis

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In past years it has become apparent that myocardial contractility is not readily assessed by standard hemodynamic measurements, such as cardiac output, left ventricular pressures, or stroke work.[1,2] Greater insight into the contractile state of the myocardium is provided when the velocity aspects of the ventricular contraction are taken into consideration. In this respect, investigations on the relationship between the velocity of contraction and tension have proved most helpful. This concept was first described in the isolated cat papillary muscle[3] and was then applied to the intact canine heart[4,5] and recently to the human left ventricle. Gault and associates have shown that during ejection at a comparable left ventricular peak tension the velocity of shortening of the contractile elements was definitely lower in patients with left ventricular myocardial disease than in a control group without myocardial dysfunction. While these findings might be expected because 7 out of 9 patients with myocardial disease had abnormal left ventricular dynamics at rest, there is considerably more controversy concerning the contractility of the heart hypertrophied by chronic pressure load. It would appear that many of the conflicting results stem from the differences in experimental procedures and measurements on which evaluation of the contractile function are based.[8-13] The most recent observations in papillary muscles from the hypertrophied right ventricle of cats[14] and in the hypertrophied intact canine left ventricle,[15] where the assessment of the contractile state was carried out by measuring factors related to the velocity of muscular contraction, show under chronic pressure load a decreased myocardial contractility.

Using a similar approach Levine[7] has evaluated left ventricular contractility in 5 patients with aortic stenosis. The maximal velocity of shortening of the contractile elements, determined by extrapolation of the inverse portion of the tension velocity curves of auxotonic systoles, was clearly diminished in those 3 patients who pro-

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Table I Left ventricular dynamics end-diastolic dimensions wall thickness muscle mass

Group	Name	Age	Diagnosis	BSA (M^2)	CI ($L./min./M^2$)	HR_{HC} ($min.^{-1}$)	HR_A ($min.^{-1}$)	SP (mm.Hg)	EDP_{HC} (mm. Hg)	EDP_A (mm. Hg)	AOP (mm. Hg)	MPG (mm. Hg)
	D U ♀	24	AVD OFO	1.51	3.7	90	78	108	10	13	108/68/84	—
	P A ♀	33	PS	1.44	2.	80	84	118	8	6	114/73/94	—
	K. H ♀	42	ASD II	1.73	3.6	80	94	120	11	—	120/76/100	—
Group 1	W M ♀	17	T a-v B.	1.51	.5	48	60	122	10	9	121/63/87	—
	M M ♀	18	DBA	1.48	3.9	90	82	102	6	10	95/60/83	—
	B A ♂	18	APW	1.64	3.5	83	75	115	8	9	110/70/87	—
	$\bar{X}$	25.3		1.65	3.3	79	79	114	8.8	—	112/68/89	—
	S.E.±	4.1		0.05	0.3	6	5	3	0.7	—	3/3/3	—
	M. C ♂	24	AS, AI	1.70	4.9	86	70	118	6	10	102/69/87	18
	G A ♂	57	AS, AI	1.70	3.5	65	70	196	12	—	151/85/109	45
	M. F ♂	43	AS, AI	2.06	3.3	74	85	156	7	—	113/64/85	40
Group 2	S. C ♂	13	AS	1.45	5.0	70	64	177	17	15	139/93/119	4
	V O ♂	44	AS, AI	1.51	2.9	57	58	161	17	16	156/65/96	16
	C. G ♂	31	AS	1.83	3.9	60	60	161	9	10	95/63/82	42
	$\bar{X}$	35.3		1.71	3.9	69	68	162	11.3	—	127/73/96	30.8
	S.E.±	6.5		0.09	0.4	4	4	11	1.9	—	10/5/6	5.3
	p 1 vs. 2	NS		NS	NS	NS	NS	<0.01	NS	—	NS	—
	M. O ♂	59	AS, AI	1.83	3.6	60	68	200	17	—	128/70/93	70
	G M ♂	59	AS	1.82	3.0	70	64	200	23	—	114/64/91	35
	N W ♂	59	AS	1.83	.3	60	68	194	14	15	137/73/93	50
Group 3	K. P ♂	35	AS, AHT	.15	4.4	48	52	201	20	—	151/88/114	33
	Z. W ♂	27	AS, AI	1.66	3.6	5	71	183	17	18	108/64/81	57
	C. G ♂	21	AS, AI	1.74	3.4	71	81	165	22	—	90/55/72	57
	$\bar{X}$	43.3		1.80	3.4	64	67	191	18.8	—	121/69/92	57.2
	S.E.±	7.2		0.08	0.3	4	4	6	1.4		9/5/6	3.3
	p 1 vs. 3	NS		<0.02	NS	NS	NS	<0.001	<0.001		NS	—
	p 2 vs. 3	NS		NS	NS	NS	NS	<0.03	<0.02		NS	<0.01

Symbols: BSA = Body surface area; CI = cardiac index; HR = heart rate during heart catheterisation; HR heart rate during angio ... pressure during angiocardiography; AOP = aortic pressure; MPG = mean systolic pressure gradient across the aortic valve; max dp/dt ... ratio of film and corrected for x-ray magnification; M = calculated short axis of the left ventricle, corrected for x-ray magnification; $\frac{L}{M}$ ratio of ... film and corrected for x-ray magnification; h = calculated wall thickness (the spherical model); ... = calculated internal left ventricular ...; ♀ = female; ♂ = male; ... = max. V_m = maximal calculated velocity of shortening of the contractile elements ... = time ... The ... listed are those measured ... APP ... = wall thickness measured in ROP; ** = all thickness measured ... APP; AVD = anomal ... defect (60% left-to-right shunt); T ... B = total block (congenital); DBA = ductus Botalli apert (20% left-to-right shunt); APW ... S.E. = standard error; NS = not significant ($p > 0.05$).

sented hemodynamic evidence of impaired left ventricular function. However, wall thickness was not measured and therefore an assessment of the contractile state per unit of left ventricular muscle mass was not possible.

In the present paper we intend to evaluate contractility per unit of left ventricular myocardium on the basis of the tension velocity relation in humans in whom hypertrophy had developed from a chronically increased impedance to left ventricular ejection but in whom no signs of left ventricular failure were observed. To investigate this we examined patients with valvular aortic stenosis who were subdivided into two groups according to the severity of the pressure load. They were

...ocity of shortening of the contractile elements and mean wall tension

...ax. dp/dt (mm. Hg/sec.)	L (cm.)	M (cm.)	L/M	EDVI (ml./M²)	h_m (cm.)	h' (cm.)	(cm.)	LVMI (Gm./M²)	EDT (Kg./cm.)	T_{mean} (Kg./cm.)	V_{max} (circ./sec.)	HV_{max} (msec.)
2,840	8.30	5.75	1.660	105	0.94	0.90	2.53	129	0.024	0.073	1.57	31
2,070*	7.65	5.40	1.415	82	1.07**	1.10	3.04	137	0.015	0.054	1.63	32
1,580	7.50	5.35	1.403	73	0.74†	0.75	3.11	60	0.031	0.054	1.23	30
2,730*	11.70	5.96	1.965	145	0.76**	0.53	3.77	123	0.030	0.067	1.39	29
2,250	10.00	5.45	1.830	103	0.90	0.93	3.34	175	0.015	0.034	1.59	23
2,450	7.45	5.45	1.370	73	1.00**	1.01	3.00	103	0.016	0.030	1.61	33
2,300	8.93	5.59	1.60	97.5	0.91	0.93	3.28	114.8	0.022	0.054	1.44	32
178	0.65	0.09	0.10	11.1	0.05	0.05	0.10	10.3	0.003	0.007	0.10	1.6
2,610	9.0	6.50	1.385	117	1.18	1.15	3.63	169	0.013	0.021	2.00	26
2,180	10.3	5.10	2.010	83	1.32†	1.33	3.27	164	0.020	0.036	1.27	42
1,640	11.9	6.35	1.870	123	1.35†	1.35	4.03	144	0.014	0.030	1.35	28
3,150*	8.95	5.20	1.720	65	1.05**	1.06	3.11	135	0.032	0.064	1.02	31
1,860*	12.25	7.20	1.700	222	1.05	1.06	4.30	230	0.047	0.063	1.04	30
2,170*	8.6	6.00	1.430	87	0.09	1.00	3.37	112	0.021	0.030	1.67	24
2,230	10.18	6.06	1.68	119.7	1.18	1.16	3.62	159	0.025	0.042	1.31	30.8
230	0.64	0.33	0.10	21.6	0.06	0.04	0.15	16.6	0.005	0.007	0.13	2.7
NS	NS	NS	NS	NS	<0.02	<0.02	NS	NS	NS	NS	NS	NS
2,950*	11.36	4.00	1.925	114	1.20†	1.4	3.74	175	0.036	0.027	1.20	31
1,850*	12.50	6.15	2.030	136	1.50†	1.63	3.60	250	0.027	0.049	1.14	67
2,130	9.30	5.30	1.790	84	1.62	1.66	3.16	232	0.018	0.030	1.61	23
2,350	11.60	6.10	1.900	105	1.53**	1.54	3.78	330	0.033	0.037	1.15	34
2,450*	9.75	6.15	1.900	53	1.58**	1.29	3.19	1.6	0.025	0.043	1.24	29
2,050	9.90	4.05	1.885	106	1.61**	1.83	3.56	232	0.035	0.048	1.32	23
2,310	10.73	5.94	1.90	105	1.45	1.48	3.55	224.2	0.031	0.040	1.30	31.2
156	0.83	0.15	0.07	8.1	0.07	0.07	0.13	26.6	0.003	0.003	0.07	6.5
NS	NS	NS	NS	NS	<0.001	<0.001	NS	<0.01	<0.05	NS	<0.05	NS
NS	NS	NS	NS	NS	<0.02	<0.01	NS	<0.05	NS	NS	NS	NS

...contractile... LVP = left ventricular peak pressure; EDP = end-diastolic pressure during heart catheterization; EDP = end-diastolic ... maximum rate of rise of left ventricular pressure; L = longest axis of the left ventricle in the right oblique projection as measured in the angio... the longest to the short axis; EDVI = end-diastolic volume determined by angiocardiography; h_m = wall thickness as measured on the angio... ...ness in the spherical model; LVMI = left ventricular muscle mass; EDT = end-diastolic tension; T_{mean} = mean wall tension at V_{max} ... dp/dt falling slightly into the ejection period; ... wall thickness measured in both anteroposterior (APP) and right oblique projection (RO?) ... [illegible] pulmonary venous drainage (?) left-to-right shunt); OFO = open foramen ovale; PS = pulmonary stenosis; ASD II = atrial septal ... aortic pulmonary window (bidirectional shunt); AS = aortic stenosis; AI = aortic insufficiency; AHT = arterial hypertension; $\bar{X}$ = mean value; ...

compared with a control group who had a normal or only slightly volume loaded left ventricle.

Three main questions arose: (1) In patients with a chronic pressure load but without signs of heart failure does the contractile state of the myocardium differ from that in normal subjects? (2) To what extent is the myocardial contractile state influenced by the severity of the pressure load? (3) What role does the age of the patient play?

Methods

Eighteen patients were examined and they were subdivided into three groups, each group comprising 6 patients. Group 1 included patients with congenital lesions

particularly affecting the right side of the heart (Table I) Since none or only a slight volume load of the left ventricle was present it was assumed that their left ventricular contractility was normal Therefore they represented the control group (Group 1) The mean age was 25 3 ± 4 1 years. Group 2 included patients with aortic stenosis (AS) who had a mean systolic pressure gradient of less than 50 mm Hg (mean 31 ± 5 mm Hg) whereas in Group 3 the gradient was higher than 50 mm Hg (mean 58 ± 3 mm Hg) The dividing point of 50 mm Hg was chosen because it is one of the guidelines for surgical correction in our hospital The mean age of the subjects was 35 3 ± 6 5 and 43 3 ± 7 7 years respectively Seven of the patients (M C G A. M F V O M O Z W and C G) with aortic stenosis had a concomitant aortic regurgitation of small or moderate degree. All patients were in sinus rhythm none had bundle branch block QRS being not longer than 0 10 sec At the *time of the study no one had signs of the* left or right heart failure One patient (V O) in Group 2 had an episode of heart failure six months prior to investigation He was digitalized and fully compensated For the purpose of separate investigation Patient C G in Group 2 received 0 5 mg of strophanthin before the angiographic measurements were performed In Group 3 one patient (K P) was included with a mean pressure gradient of less than 50 mm Hg but he showed an arterial hypertension of 170/110 mm Hg

All patients were studied in the fasting state. Five milligrams of Valium* or 10 mg of Librium* were given orally one hour before the examination Right and left heart catheterization followed by cine angiocardiography was carried out on all patients Right heart catheterization was performed with a Cournand No 7 Fr catheter via the right femoral vein Left heart catheterization was performed with a Brockenbrough† catheter by transseptal puncture. In Group 1 in two patients (D U and K H) a catheter tip manometer‡ was introduced via the left axillary vein and passed through an open foramen ovale and an atrial septal defect respectively into the left ventricle A red Oedman catheter was advanced to the ascending aorta through the femoral artery Pressures were recorded by external Statham transducers P23Db and left ventricular end-diastolic pressure (EDP) was determined after the a wave Cardiac output was measured by the thermodilution method [16,17] Ice-cold saline was injected into the left ventricle and sampling was performed by a thermistor bead positioned 2 cm above the aortic valves. All recordings were made on an Electronics for Medicine 8 channel oscillograph

The first derivative of the left ventricular pressure (dp/dt) was obtained from the pressure curves recorded through the Brockenbrough catheter This catheter was connected by a stiff Teflon tubing to an external Statham transducer all pressures were recorded at a cut-off frequency of 15 cycles per second to remove artifact [18] The *time constant of the RC-differentiating* circuit was 0 5 msec.

Since the frequency response of the employed catheter manometer system is open to criticism in view of a meaningful estimation of the quotient $\frac{dp/dt}{P}$ on which calculation of the instantaneous velocity of shortening of the contractile elements is based (vide infra) $\frac{dp/dt}{P}$ was calculated throughout the isovolumic part of the systole in 12 left ventricular pressure curves simultaneously recorded by the Brockenbrough-stiff Teflon system and by a Statham SF 1 tip manometer For this purpose dp/dt of the two pressure curves was determined at several selected isovolumic pressure values (P) identical for both curves These measurements were carried out in 4 additional patients (3 with coarctation of the aorta and one with an uncomplicated atrial septal defect) Eight curves were obtained during sinus rhythm or right atrial pacing and 4 from postextrasystolic beats. From Fig 1 it is evident that $\frac{dp/dt}{P}$ of the Brockenbrough tracings was

*F Hoffmann-La Roche and Co. AG Basel, Switzerland.
†United States Catheter and Instrument Corp., Glens Falls, N Y
‡TELCO, Gentilly sur Seine, France.

*Elma, Sweden.

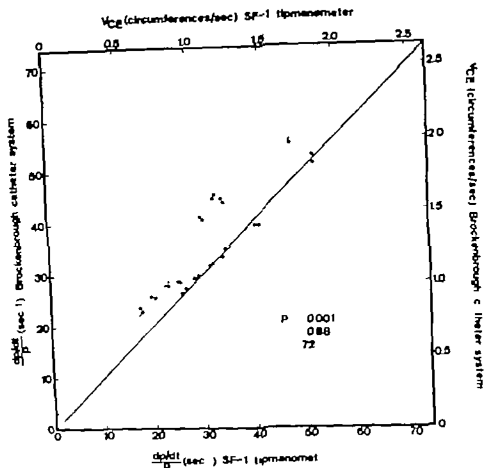


Fig. 1. Comparison of $\frac{dp/dt}{P}$ of the Brockenbrough catheter-Teflon connector-external Statham P23Db system with $\frac{dp/dt}{P}$ of Statham SF 1 tip manometer. Seventy-two paired observations were carried out in 12 left ventricular pressure curves recorded simultaneously by both systems. There was systematic overestimation of $\frac{dp/dt}{P}$ by the Brockenbrough catheter system. On the average, the error of overestimation was 19 per cent but its magnitude was fairly constant within the range of the velocities studied. In the scales on the top and on the right, $\frac{dp/dt}{P}$ was converted to velocity of shortening of the contractile elements by dividing $\frac{dp/dt}{P}$ by the coefficient of series elasticity (28 cm.⁻¹). dp/dt = Rate of rise of left ventricular pressure. P = left ventricular pressure.

systematically larger than the quotient obtained from the tip-manometer curves. Since the intercept of the linear regression line with the y-axis is small the error of overestimation does not, however vary substantially throughout the range of instantaneous velocity of shortening extending from 0.6 to 2.0 circumferences per second. On the average the error of overestimation was 19 per cent. The range of the velocities observed in the present study was similar to that in the 4 additional patients. In summary then it is recognized that in absolute terms the velocities of shortening determined from the Brockenbrough tracings are overestimated however this overestimation should not invalidate comparisons between the three groups of patients since the error was a systematic one and was of similar magnitude through

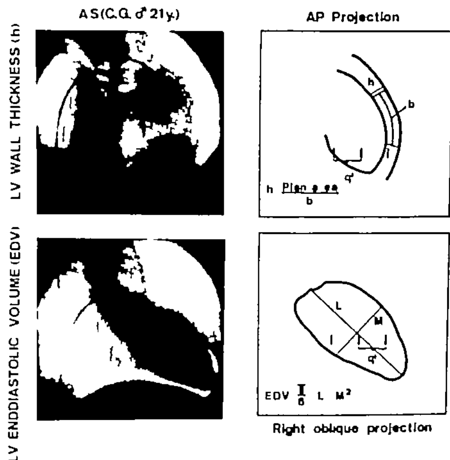


Fig 2 Left ventricular cineangiograms in a patient of Group 3 Measurement of the wall thickness (above) and of the end-diastolic volume (below) L is the long axis covering the longest diameter from the base to the apex. M represents the short axis which was calculated from the formula $M = \frac{4}{L} \cdot \frac{1}{\pi}$ q is the projected distance between markers of the grid

out the range of the observed values of velocity

Following heart catheterization the patients were transferred to the x ray department for cineangiocardiography With the patient in the right-oblique and antero-posterior positions, contrast material (Ronpacon 440*) was injected by a Contrac high speed injector† into the left ventricle or the left atrium The amount injected varied between 8 and 27 ml (average 15 ml) and injections were made on end inspiration Cineangiograms were exposed at 50 frames per second on 35 mm cine angiofilm During the cineangiogram the electrocardiogram and left ventricular or aortic pressures were recorded on an Elema EM 8 direct writer

On the cinefilms the following measurements were made (1) left ventricular end diastolic volume (EDV) in the right-oblique projection (2) thickness of the left ventricular wall (h) determined in the middle third of the lateral portion either in the right oblique (5 patients) or the antero-posterior projection (7 patients) In 6 patients h was measured in both projections there was no significant difference between the two values of wall thickness ($p < 0.5$) Injections with extrasystoles were discarded

For the determination of EDV and h the film was projected onto a frosted glass screen The internal and external contours of the left ventricle were outlined on a sheet of paper affixed to the screen The area of the left ventricular end-diastolic silhouette (in right-oblique projection) and the wall section of the middle third of the left ventricle (in the anteroposterior projection)

*Cilag AG, Schaffhausen, Switzerland.
†Siemens AG, Dept. SRW Zurich, Switzerland.

were obtained by planimetry (Fig 2). Corrections for x ray magnification were achieved by means of a filmed scale.

Correction for distortion of the cinepicture due to nonparallel x ray beams was obtained by calculating the average of at least two marker distances (q) within the silhouette of the left ventricle (Fig 2).

The left ventricular end-diastolic volume was calculated from the one plane cineangiograms, assuming that the chamber can be represented by an ellipsoid of revolution. The following formula was used

$$EDV = \frac{\pi}{6} \quad LMN$$

L being the long and M and N the short axes of the ellipsoid. For our calculations it was assumed that the short axis, which is not visible but perpendicular to both L and M is equal to M. The formula then becomes

$$EDV = \frac{\pi}{6} \quad LM$$

The long axis L was measured as the maximal length in the right-oblique projection and the short axis M was calculated according to the formula

$$M = \frac{4}{\pi} \quad \frac{A}{L}$$

where A is the planimetered area in the right-oblique projection. A correction for the volume of trabeculae carneae and papillary muscles[21-23] was not carried out.

The left ventricular muscle mass (LMM) was derived from the left ventricular muscle volume (LMV) and the specific density of heart muscle (1.05)

$$LMM = LMV \quad 1.05$$

LMV was calculated as the difference between the total left ventricular volume and the EDV

$$LMV = \left[\frac{4}{3}\pi\left(\frac{L}{2} + h\right) \quad \left(\frac{M}{2} + h\right)\right] - EDV$$

Calculation of the instantaneous stress velocity relationship throughout the isovolumic phase of the left ventricular systole. For mathematical simplicity a spherically shaped left ventricle was assumed. The developed mean left ventricular wall stress (T) in kilograms per square centimeter was thought to be most closely approximated[24] by the formula

$$T = \frac{p}{2} \quad \frac{r_i}{h}$$

where p is the actively developed left ventricular pressure, r_i the internal radius of the assumed spherical left ventricle and h' the calculated wall thickness. r_i was obtained from the formula

$$= 3\sqrt{\frac{3}{4} \quad \frac{EDV}{\pi}}$$

and h was calculated as the difference between the external radius of the spherical left ventricle

$$r = 3\sqrt{\frac{3\,(EDV + LMV)}{4 \quad \pi}} \text{ and } r_i$$

Since for a given volume, the surface of a sphere is smaller than that of an ellipsoid it is obvious that h is slightly larger than the measured wall thickness h (Table I). Throughout this paper the words "stress" and "tension" are used synonymously.

Velocity of shortening of the contractile elements (V_{CE}) was obtained by the formula given by Taylor and associates[25,26]

$$V_{CE}\ (circumferences/sec.) = \frac{dp/dt}{K \quad P}$$

where dp/dt is the rate of rise of left ventricular pressure, K the coefficient of series elasticity assumed to be 28 cm.$^{-1}$ [26] and P the left ventricular pressure. Stress and V_{CE} were calculated at several points throughout the isovolumic phase of the left ventricular systole. V_{max} is defined as the calculated maximal velocity during the isovolumic phase. It should be stressed that this is *not* the extrapolated maximal velocity of shortening at zero load. The time interval required to reach V_{max} ($t\,V_{max}$) was measured from the point where the left ventricular pressure began to rise after the a wave up to V.

End-diastolic pressure measured during heart catheterization in the patients included in this study did not differ more than 4 mm. Hg and the heart rate not more than

*In Table I LMM is given as normalized value for 1 M.² of body surface area (LMMI).

14 beats per minute from the values obtained during angiocardiography There was no directional difference (Table I) For statistical comparison of the tension velocity curves between the three groups, mean values of V_{CE} at identical stresses were calculated The difference between these mean values was assessed by using the Student t test. Throughout the paper mean values are given ± 1 S E

Results

The findings are summarized in Table I

Hemodynamics No difference was found between the three groups as to the mean values for cardiac index heart rate end diastolic volume aortic pressure and maximum dp/dt. Concerning the EDV there is one abnormally high value in Patient V O of Group 2 who had an EDV of 222 ml per square meter He had been digitalized for several months after an episode of left heart failure. As to EDT no significant difference was found between Groups 1 and 2 whereas a significant difference exists between Groups 1 and 3 ($p < 0.001$) and between Groups 2 and 3 ($p < 0.02$) The left ventricular peak pressure was significantly increased in the pressure-loaded groups and the highest values were recorded in Group 3 (p 1 vs. 2 < 0.01 p 1 vs. 3 < 0.001 p 2 vs. 3 < 0.05)

Wall thickness (h') and left ventricular muscle mass (LVMM) The mean value for calculated wall thickness is 0 93 ± 0 05 (S E.) cm in Group 1 1 16 ± 0 06 cm in Group 2 and 1 48 ± 0 07 cm in Group 3 The difference is significant between all three groups (p 1 vs. 2 < 0.02 p 1 vs. 3 < 0.001 p 2 vs. 3 < 0.01) Parallel to the increase in wall thickness an increase in muscle mass is seen with mean values of 114 8 ± 10 3 Gm per square meter for the control group 156 8 ± 16 6 in Group 2 and 234 2 ± 26 4 in Group 3 Significant differences exist between Groups 1 and 3 ($p < 0.01$) and Groups 2 and 3 ($p < 0.05$)

Stress and velocity Concerning left ventricular end-diastolic wall stress (EDT) a significant difference exists only between the values of Groups 1 and 3 ($p < 0.05$) whereas no difference is seen between Groups 1 and 2 and between the two pressure loaded groups. The stress at the

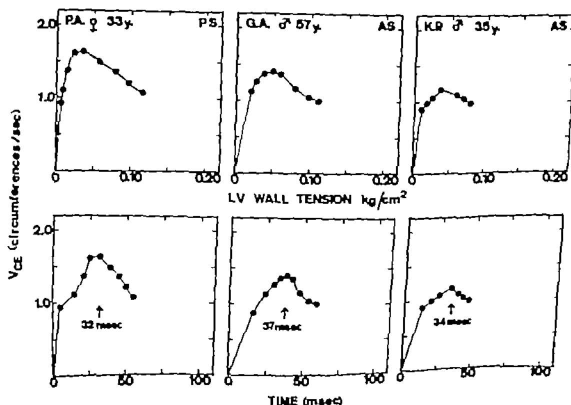


Fig. 3 Tension-velocity and time-velocity relations in one patient of each group. The arrows indicate the point of V_{max} and the number below the interval t V_{max} PS = Pulmonary stenosis AS = aortic stenosis.

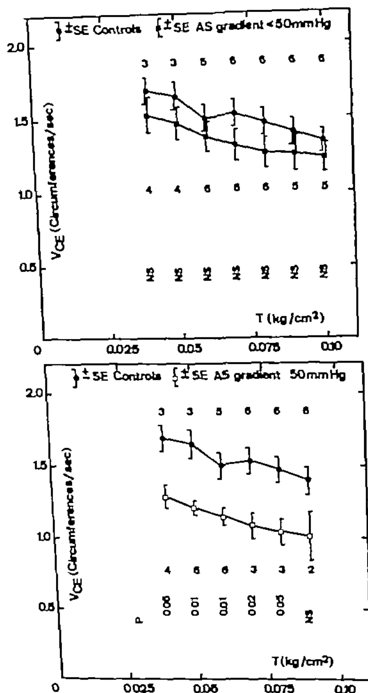


Fig. 4. Tension-velocity relation in the control group and in patients with aortic stenosis with pressure gradient of below (top) and above 50 mm. Hg (bottom) respectively. Mean values and standard error for V_{CE} at given tension in Group 1 (●), Group 2 (■) and Group 3 (□) respectively. Numbers above and below the curves = number of observations for given point.

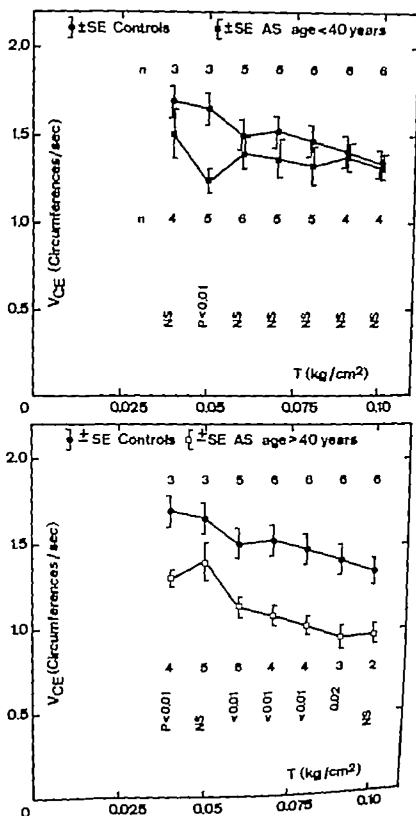


Fig. 5 Tension-velocity relation in the control group and in patients with aortic stenosis separated according to their age. Mean values and standard error for V_{CE} at a given tension in the control group and in patients under 40 years of age (top) and in those over 40 years of age (bottom). Numbers above and below the curves = number of observations for a given point.

moment of the calculated maximal velocity (T_{Vmax}) is within the same range for all three groups with values of 0.051 ± 0.007, 0.042 ± 0.007 and 0.040 ± 0.003 kg. per square centimeter respectively. The calculated V_{max} in Group 2 was slightly but not significantly smaller than in Group 1. In Group 3 V_{max} was, however, significantly lower than in the control subjects ($p < 0.05$). No statistically significant difference existed between Groups 2 and 3. Fig. 3 shows the tension velocity curves of one representative subject of each group. There is no difference in the shape of the curves. It is obvious, however, that V decreases with increased pressure load. Concerning the time to maximal velocity (tV_{max}) similar results are found in all three groups with mean values of 31, 30 and 31 msec. respectively (Table I, Fig. 3). The state of the myocardium in the three groups, as evidenced by the tension velocity relation is given in Fig. 4. The mean values of V are plotted versus given tensions. In all three groups the tension-velocity curves are similarly shaped. Although the mean values are clearly separated no significant difference exists between Groups 1 and 2 as there is extensive overlap in individual values. In contrast to these findings, a significant difference can be demonstrated between the control subjects and the patients with a pressure gradient above 50 mm. Hg, the curve of Group 3 being shifted to the left and downward with respect to the control group. This significant difference comprised all values except the V_{CE} for a tension of 0.09 kg. per square centimeter (Fig. 4). Since at this particular tension only two values were available for comparison in Group 3 statistical evaluation is questionable. Again no significant difference existed between the two groups with pressure loads although the mean values were clearly separated (Fig. 4).

In plotting the tension-velocity relationship under the aspect of age a significant difference between the control group and the patients over 40 years of age (53.3 ± 3.2 years) irrespective of the extent of the pressure gradient in the latter group was observed (Fig. 5). However, no distinction became apparent between the control group (25.3 ± 4.1 years) and the patients under 40 years of age (25.2 ± 3.2 years) and between the two patient groups. The mean pressure gradient in the age groups was 40 ± 7 mm. Hg and 46 ± 7 mm. Hg respectively ($p < 0.6$). The hemodynamic findings in both age groups showed no significant differences except the cardiac index which was 4.2 L. per minute per square meter in the group under 40 years and 3.1 L. per minute per square meter in the group over 40 years ($p < 0.01$).

Discussion

Instantaneous tension velocity relationship. Standard hemodynamics as cardiac index, aortic pressure, and left ventricular end-diastolic volume per square meter do not permit a separation of the controls and the patients with aortic stenosis, i.e., a chronic pressure load. The higher EDP in Groups 2 and 3 are not indicative of a diminished left ventricular function in the presence of an increased left ventricular muscle mass.[24] Maximum dp/dt at similar left ventricular end-diastolic dimensions and heart rates failed to demonstrate a difference in left ventricular function between the three groups, although this parameter has been shown to be useful for the assessment of contractility of a given heart under different hemodynamic conditions both in man and dog.[27-29] One should bear in mind, however, that in the present study not all measurements of maximum dp/dt are meaningful because in some patients maximum dp/dt fell slightly into the beginning of the ejection phase. As pointed out by Covell and associates[1] and Ross and co-workers, the instantaneous tension velocity relationship allows for a more complete definition of the abnormalities of the left ventricular myocardium than do routine hemodynamic measures. In man the application of the tension-velocity relationship to the intact left ventricle as carried out in this study is by no means free of controversy.

One prerequisite for the calculation of V_{CE} is to know the modulus of elasticity. This modulus is related by a constant (K) to the load during contraction. In the cat papillary muscle K amounts to 28 cm.$^{-1}$ [8] Similar values were found in the intact normal dog heart.[30] In humans K has not yet been determined. For this reason, the

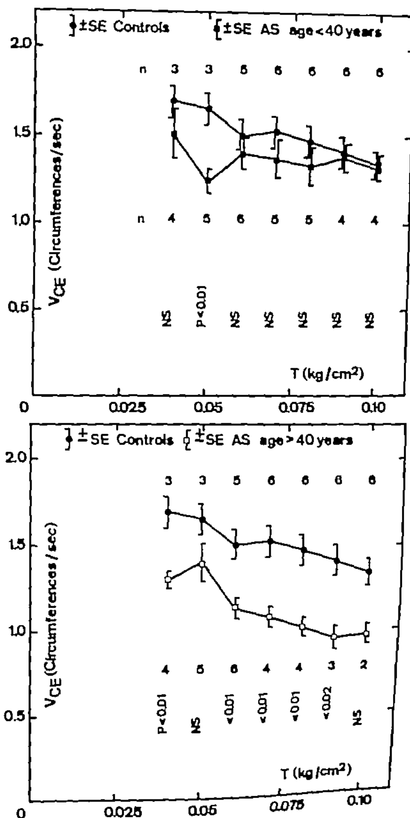


Fig 3 Tension-velocity relation in the control group and in patients with aortic stenosis separated according to their age. Mean values and standard error for V_{CE} at a given tension in the control group in patients under 40 years of age (top) and in those over 40 years of age (bottom). Numbers above and below the curves = number of observations for a given point.

ventricles. Since the semiaxis ratios within the three groups did not differ significantly it is obvious that virtually no relative error in stress calculation between the three groups existed.

During the early phase of the isovolumic contraction the rise of tension was associated with an increase of V_{CE} (Fig 3). The delay of about 30 msec. for V_{CE} to reach its maximum ($t - V_{max}$) may be caused by (1) time necessary for electrical activation and for effective synchronization of the musculature of the left ventricle and/or (2) delayed onset of active state in heart muscle. In the isotonically contracting cat papillary muscle, *norepinephrine* produced an increase in the rate of onset of active state which was evidenced by the shortening of the time to peak velocity.[34] On the other hand achievement of maximal V_{CE} in the acutely failing isovolumically beating dog heart was delayed.[5] In the present study there was no significant difference in the time to peak V_{CE} between the three groups, the mean values ranging from 30 to 32 msec. Since no major abnormalities in electrical activation as judged from the duration of the QRS complex, were present, it is likely that the rate of onset of active state is similar in both controls and hypertrophied left ventricles. This does not imply however that the intensity of active state, i.e. the level of *myocardial contractility is the* same in all three groups the diminished contractility in the most severely pressure-loaded patients (Group 3) is clearly displayed by the shift to the left and downward of the tension-velocity curve (Fig 4). These observations are in accordance with the results obtained by Spann and associates[14] in hypertrophied cat papillary muscles. The unaltered time to peak isometric tension in these in vitro studies suggests a normal rate of onset and a normal duration of active state in the hypertrophied muscle. The force-velocity relationships, however clearly indicate that contractility was reduced in the muscles obtained from the hypertrophied right ventricles.

In the present study time to peak velocity was slightly shorter than in a group of 16 patients with uncomplicated atrial septal defect[35] in whom it averaged 41 ± 2 (S.E.) msec. This somewhat longer interval may be due to a slight disturbance in ventricular activation on account of the presence of an incomplete right bundle branch block in the majority of the cases with ASD II. A much longer interval (measured from end-diastole to peak isovolumic V_{CE}) was recently reported by Fallen and Gorlin.[36] In normal subjects time to peak velocity amounted to 65 msec. The reason for the discrepancy in our observations is not entirely clear. It may stem from a different method or procedure of timing the commencement of the interval.

Left ventricular hypertrophy and myocardial contractility. In experimental hypertrophy produced by a chronic pressure load the assessment of the contractile state of the myocardium as based upon velocity parameters has given evidence in vitro and in vivo that the hypertrophied but not failing myocardium exhibits a lower inotropic state than the normal heart muscle.[14,15,37] Compared to the situation in human aortic stenosis these experimental investigations dealt with relatively short lived outflow impedance of several weeks or months. Thus, the results can be applied only with great reserve to the human myocardium subjected for a much longer period of time to a chronic pressure load. In the present study left ventricular hypertrophy was demonstrated by an increased left ventricular wall thickness and an enhanced muscle mass per square meter of body surface area in Groups 2 and 3 as compared to the control group. The magnitude of left ventricular hypertrophy was related to the severity of the pressure load as evaluated by the aortic left ventricular pressure gradient. The greatest wall thickness and the highest muscle mass were observed in Group 3 with the highest pressure load. The patients with a smaller pressure load (gradient < 50 mm Hg) elicited a less markedly increased wall thickness and left ventricular muscle mass. With respect to the contractile state, the subjects with the highest pressure load and the most pronounced left ventricular hypertrophy (Group 3) showed a reduced contractility. This was indicated by a significantly decreased V_{max} at a similar preload (end-diastolic volume) and mean wall tension as in Group 1 (Table I) and by a significant shift of the tension velocity curve to the left and downward (Fig 4). In

use of a K value of 28 cm^{-1} for the calculation of V_{CE} is debatable. Gault and associates[8] in a recent study on the contractility in normal and failing human left ventricles did not calculate V_{CE} throughout the cardiac cycle as the coefficient of series elasticity is assumed to differ between normal and failing hearts This objection certainly applies to the hearts of patients with left ventricular myocardial disease in which alterations in the histological structure of the myocardium are to be expected In dogs with left ventricular scars from experimental myocardial infarction the highest value for K was 13 7 cm^{-1}[31] On the other hand Parmley and co-workers[32] reported that induction of ventricular hypertrophy did not alter the series elasticity in the cat papillary muscle Since in our patients with aortic stenosis the main stems of the coronary arteries, as displayed after injection of contrast dye into the aortic root were free of stenosis or plaques and since the ECG did in no case reveal signs of old or recent myocardial infarction we felt justified in assuming that in both Groups 2 and 3 the left ventricular myocardium was hypertrophied without major scars like those following the occlusion of a main coronary artery[31] which would alter substantially the K value Then the use of a K value of 28 cm^{-1} does not appear to represent an important source of error in the calculation of V_{CE} in the present study

In the isolated cat papillary muscle contracting under afterloaded conditions and in the isovolumically beating intact left ventricle it has been demonstrated that the maximal velocity of shortening at zero load is a direct measure of the level of contractility[1,4,5] This particular value of V_{CE} cannot be determined experimentally but has to be obtained by extrapolation of the tension velocity curve to the velocity axis. In order to obviate a difficult extrapolation from the sometimes very short section of the inverse portion of the tension velocity curves, the assessment of the contractile state was based solely on calculated values of V_{CE} Throughout the isovolumic phase the calculated velocities of the three groups were compared at given tensions with values ranging from 0 04 to 0 09 Kg per square meter (Fig 4) It should be stressed however that only those values of V_{CE} were used which were obtained after the individual V_{max} was reached In so doing no values were included for comparison before the active state was fully developed Since EDV and presumably the end-diastolic fiber length were similar in all three groups, the course of the tension velocity curves could be assumed to be determined only by the state of contractility Thus, the significantly lower velocities in Group 3 compared with the controls at identical tensions are indicative of an impaired contractile state in Group 3 On the other hand taking EDP or EDT as indices of preload the tension velocity curves in Groups 2 and 3 should be shifted to the right of the control curve since EDP and EDT were significantly higher under chronic pressure load As a shift to the left and downward was noted in Groups 2 and 3 the decreased left ventricular contractility in the pressure loaded hearts becomes more pronounced

A further objection to comparing left ventricular dynamics between control subjects and patients with a chronic pressure load could be a different geometry of the left ventricle in the three groups, despite a similar left ventricular EDV per square meter However the end-diastolic angiographic silhouette of the left ventricle did not display major differences in shape for the three groups. This is instanced by the mean values of the semiaxis ratios that were not significantly different in the three groups (Table I) It is recognized that the mean wall stress of a spherically shaped ventricle as assumed for mathematical purposes in the present study is underestimated when compared to the wall stress in an ellipsoidal left ventricle. At a given end-diastolic volume and wall thickness the magnitude of the underestimation of the wall stress in the spherical model depends upon the ratio of the major to the minor semiaxis in the ellipsoidal model According to Graham and associates[27] wall tension in an ellipsoidal model with semiaxis ratios of 2 1 1 to 1 4 1 is 8 per cent and 3 per cent respectively higher than in a spherical model The largest semiaxis ratio in our study was 2 03 1 the smallest 1 37 1 Although our calculations of wall stress were subject to a systematic underestimation a maximal relative error of about 5 per cent had to be considered when comparing wall stresses of individual

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Group 2 (Fig 4) the tension velocity curve was slightly displaced to the left and downward as compared to the curve obtained from the control subjects However this shift was not significant It would then appear that the level at which the chronic pressure load in aortic stenosis leads to a definitely decreased left ventricular contractility may reside at a pressure gradient of about 50 mm Hg

The severity of the left ventricular pressure load and the resulting hypertrophy were not however the only factors that determined the inotropic state of the myocardium By grouping the patients with aortic stenosis according to their age it was observed that those over 40 years had a significantly reduced myocardial contractility compared with the control subjects (Fig 5) On the other hand no significant difference existed between the controls and the patients less than 40 years of age (Fig 5) It should be stressed that the aortic left ventricular pressure gradient was similar in both groups ranging from 15 to 70 (mean 46) mm Hg in the group over 40 years and 19 to 57 (mean 40) mm Hg in the group under 40 years Similarly the left ventricular wall thickness and muscle mass per square meter of body surface area were not significantly different in the two groups These findings suggest that at a comparable level of myocardial hypertrophy the contractile state of the myocardium is more compromised in the older than in the younger patients

In conclusion it can be said that (1) the contractile state of the hypertrophied left ventricular myocardium in patients with chronic pressure load from aortic stenosis but without signs of heart failure is diminished as compared to the controls (2) a significant impairment of left ventricular contractility is evident in the range of a pressure gradient of 50 mm Hg or more (3) the contractile state of the hypertrophied heart is not only dependent upon the severity of the pressure load but is also influenced by the age of the patients

Summary

Left ventricular dynamics and contractility were studied in 6 patients with assumed normal myocardial function (Group 1) and in 1? patients with aortic stenosis of a different degree separated into two groups Group 2 with a mean systolic pressure gradient of below 50 mm Hg and Group 3 with one of above 50 mm Hg None of the patients showed signs of left heart failure Routine hemodynamic parameters (cardiac index left ventricular pressure rate of rise of left ventricular pressure, and aortic pressure) were evaluated in all three groups. End-diastolic volume (*EDVI*) left ventricular muscle mass (*LMMI*) and mean left ventricular wall thickness (h) were determined by angiocardiography The following values were obtained Group 1 *EDVI* 98 ± 11 (S E.) ml/M² *LMMI* 115 ± 10 Gm/M² h 0 91 ± 0 05 cm Group 2 *EDVI* 120 ± 22 ml./M² *LMMI* 157 ± 17 Gm./M² h 1 15 ± 0 06 cm Group 3 *EDVI* 105 ± 8 ml/M² *LMMI* 234 ± 26 Gm/M² h 1 45 ± 0 07 cm The left ventricular contractile state was characterized by the instantaneous tension velocity relationship throughout the isovolumic phase of the systole It could be shown that the tension velocity curve of patients with a pressure load is shifted downward and to the left compared with the curve of the controls. This shift was only significant, however between Groups 1 and 3 By grouping the patients with aortic stenosis according to their age two pressure-loaded groups with similar mean pressure gradients could be compared with the control group Here again the tension velocity curve was shifted to the left and downward with increasing age. This change was only significant if one compared the older age group with the control group The present data suggest that the intrinsic contractile state of the myocardium of the left ventricle is impaired in patients with left ventricular hypertrophy from aortic stenosis but without heart failure It would appear that the decrease in contractility is caused both by the severity of the pressure load and by the patient s age

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Phasic right atrium and superior vena cava flow velocity in patients with tricuspid insufficiency

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The presence of hemodynamically significant tricuspid insufficiency is usually recognized by auscultatory findings,[1-3] by radiological evidence of right atrial enlargement, and by the abnormalities in the contour of the pressure curves recorded in the right atrium (RA), superior vena cava (SVC), jugular vein, and other venous beds,[4-6] and by angiographic evidence of retrograde opacification of the right atrium during angiography when the contrast agent is injected into the right ventricle. Some investigators have questioned the validity of the contour changes in the direct or indirect pulse tracings. To our knowledge, there has been no report on the direct measurement of phasic RA and/or SVC flow velocity in patients with this valvular disease state. In our previous reports, we indicated that the Doppler flowmeter–catheter system could be used to measure RA- and SVC-flow velocities in normal subjects and in patients with cardiac dysfunctions.[6-10] This Doppler technique also has been used to study the abnormalities of aortic flow velocity in patients with cardiac arrhythmias[11] and peripheral arterial flow velocity in a variety of cardiovascular conditions.[12,13]

The purpose of this paper is to describe the wave form of the telemetry of instantaneous phasic RA and SVC flow velocities using the Doppler flowmeter catheter system in patients with tricuspid insufficiency.

Material and methods

Fifty-two patients were studied and divided into 3 groups.

Group 1, control. This group included 21 normal subjects ranging in age from 18 to 45 years. All had sinus rhythm. These patients were subjected to cardiac catheterization because they were suspected to have organic heart disease based on the presence of systolic murmurs. Subsequent studies, however, which included right and left heart catheterizations, selective indicator-dilution curves, and selective cineangiocardiograms, did not reveal any hemodynamic abnormalities and the murmurs were classified as functional.

Group 2, tricuspid insufficiency. The 15 patients in this group had well-documented clinical and laboratory evidence of tricuspid insufficiency; their ages ranged from 24 to 61 years with an average of 47 years. In addition to tricuspid insufficiency, all

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Phasic right atrium and superior vena cava flow velocity in patients with tricuspid insufficiency

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The presence of hemodynamically significant tricuspid insufficiency is usually recognized by auscultatory findings,[1-3] by radiological evidence of right atrial enlargement, and by the abnormalities in the contour of the pressure curves recorded in the right atrium (RA), superior vena cava (SVC), jugular vein, and other venous beds,[4-8] and by angiographic evidence of retrograde opacification of the right atrium during angiography when the contrast agent is injected into the right ventricle. Some investigators have questioned the validity of the contour changes in the direct or indirect pulse tracings. To our knowledge, there has been no report on the direct measurement of phasic RA and/or SVC-flow velocity in patients with this valvular disease state. In our previous reports, we indicated that the Doppler flowmeter–catheter system could be used to measure RA and SVC flow velocities in normal subjects and in patients with cardiac dysfunctions.[10-12] This Doppler technique also has been used to study the abnormalities of aortic flow velocity in patients with cardiac arrhythmias[13] and peripheral arterial flow velocity in a variety of cardiovascular conditions.[14,15]

The purpose of this paper is to describe the wave form of the telemetry of instantaneous phasic RA and SVC flow velocities using the Doppler flowmeter–catheter system in patients with tricuspid insufficiency.

Material and methods

Fifty-two patients were studied and divided into 3 groups.

Group 1, control. This group included 21 normal subjects ranging in age from 18 to 45 years. All had sinus rhythm. These patients were subjected to cardiac catheterization because they were suspected to have organic heart disease based on the presence of systolic murmurs. Subsequent studies, however, which included right and left heart catheterizations, selective indicator-dilution curves, and selective cineangiocardiograms, did not reveal any hemodynamic abnormalities and the murmurs were classified as functional.

Group 2, tricuspid insufficiency. The 15 patients in this group had well-documented clinical and laboratory evidence of tricuspid insufficiency; their ages ranged from 24 to 61 years with an average of 47 years. In addition to tricuspid insufficiency, all

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Table I Clinical and hemodynamic data

Patient No	N Y class	ECG	Valvular lesion	RA (a-v mean)	RV (S/D)
1	III	SR RVH RAH LAH	MS TI	9/8/7	65/7
2	II	AF RAD	MS TI	–/12/16	40/16
3	III	AF RVH	MS TI	–/5/8	90/5-8
4	III	AF RAD	MS, TI	/7/12	45/12
5	III	AF RAD	MS TI	–/10/8	45/10
6	II	AF RVH	MS MI TI	–/15/11	76/11
7	II	SR RAH LVH	MI TI	4/1/8	34/8
8	IV	AF RVH	MS MI TI	–/11/9	45/9
9	IV	AF RVH	MS MI TI	–/12/8	60/8
10	III	AF RVH LVH	MI TI	–/12/8	120/8-12
11	III	SR RVH LAH	MS MI TI	–/7/3	35/3
12	IV	AF RVH	MIE valve prosthesis, TI	–15/13	65/13
13	II	AF	MS TI	–/5/4	42/5
14	III	AF RVH	MS, TI	–11/ /7	75/7
15	IV	AF RVH	MS MI TI	–/13/18	50/18

Abbreviations. M Male F female RA, right atrium; RV right ventricle PA, pulmonary artery; LV left ventricle CI cardiac i
SR, sinus rhythm; RVH right ventricular hypertrophy RAH right atrial hypertrophy LAH left atrial hypertrophy; AF atrial fibril

had clinical and laboratory evidence of other valvular heart disease Three patients had sinus rhythm and 12 had atrial fibrillation The clinical diagnosis of valvular heart disease was confirmed by right and left heart catheterization selective indicator-dilution curves and selective cineangiography Tricuspid insufficiency was recognized by selective cineangiocardiography with injection of a contrast agent into the right ventricle in these patients the radiopaque media regurgitated into the RA during several ventricular systoles all had large RA In 10 of the 15 patients the diagnosis of tricuspid insufficiency was also confirmed at the time of operation by the presence of a regurgitant systolic jet palpated in the RA the operations were performed to correct associated mitral stenosis and/or insufficiency Tricuspid insufficiency in these 15 patients was considered to be secondary to pulmonary hypertension and/or right ventricular failure in 13 of the 15 cases. In the remaining 2 of 15 the valvular lesion was thought to represent organic involvement of the tricuspid valve secondary to rheumatic heart disease. The clinical and hemodynamic findings in these patients are summarized in Table I The etiologic diagnosis in all cases in this group was considered to be due to rheumatic heart disease

Group 3 transient tricuspid insufficiency due to cardiac arrhythmias There were 16 patients in this group they had either transitory or permanent cardiac arrhythmias. The majority had atrial or ventricular extrasystoles 6 patients had ventricular tachycardia and 4 had complete heart block Fourteen of these 16 patients had aortic and/or rheumatic mitral valvular disease none had evidence of permanent tricuspid insufficiency The above cases were included in this report because tricuspid insufficiency was thought to have been temporarily present during the arrhythmic episode

SVC and RA flow velocity Lead II of the electrocardiogram (ECG) the phonocardiogram SVC RA or pulmonary artery pressures and left ventricular or aortic pressures were recorded simultaneously Pressures were obtained with a saline-filled No 6 or 7 end lumen catheter connected to a Statham P23Db strain gauge. Cardiac output was measured with indi

Pressures (mm. Hg)				CI (L./min./M²)	SI (ml./beat/M²)	Heart rate (beats/min.)
PA (S/D/mean)	PA "wedge" (a-v mean)	LV (S/D)	Aorta (S/D/mean)			
65/22/38	28/35/25	120/10	120/70/90	3 1	44	70
40/18/25	26/15/18	120/12	120/70/90	2 0	20	66
90/30/60	30/20/25	100/13	100/50/80	1 4	18	78
45/25/35	35/10/18	140/7	140/70/100	2 4	36	68
45/18/30	30/22	150/15	150/80/100	2 5	36	69
6/40/56	53/42	120/10	120/80/95	—	—	126
1/4/7	4/6/5	95/5	95/50/75	2 5	41	60
5/17/30	33/25	130/11	135/85/100	1 7	25	68
0/30/45	45/28	120/12	120/75/100	3 5	45	78
0/35/65	/70/35	130/30	130/60/80	1 6	24	68
5/10/20	–/28/15	120/8	120/60/70	2 4	35	63
5/30/45	/35/35	95/27	95/70/80	1 2	—	74
12/30/33	–/30/27	110/5	110/60/92	2 1	27	75
75/35/45	42/20/32	140/10	140/75/100	2 1	18	110
50/18/35	40/15/25	140/12	140/80/95	—	—	104

...ECG, electrocardiogram; MS, mitral stenosis; MI, mitral insufficiency; TI, tricuspid insufficiency; S, systolic; D, diastolic; ... right axis deviation; LVH, left ventricular hypertrophy.

cator dilution technique using indocyanine green as an indicator (Cardio-Green, Westcott, Dunning Laboratories). The indicator in an amount of 3.1 mg., was injected as a bolus into the pulmonary artery with continuous sampling (speed of 38.2 ml. per minute) from the left ventricle or ascending aorta.

Measurement of the SVC or RA-flow velocities were obtained in all cases using the Doppler catheter flowmeter telemetry system developed by Stegall and associates[1] (supplied by the Southwest Research Institute, San Antonio, Texas). This catheter flowmeter system has been used to measure blood flow velocities in our laboratory in over 250 patients for the past 2 years.[11] Detailed description of this catheter has been reported by the Stegall group. The flowmeter–catheter was connected to the Doppler ultrasonic flowmeter developed by Franklin and associates[1,3] and details of this technique have been previously described. The flowmeter–catheter was inserted into the right medial antecubital or brachial vein after the vessel had been surgically exposed at the level of the right antecubital fossa. The procedures were done under local anesthesia (Carbocaine 1 per cent, *Winthrop Laboratories*); the patients were all postabsorptive and nonsedated. Under fluoroscopic control the catheter was passed to the SVC or RA where measurements of flow velocity were obtained. In two cases, simultaneous measurements of flow velocity in the RA and in the ascending aorta using two separate flowmeter–catheter systems were obtained. In 3 patients, measurements of inferior vena cava and suprahepatic vein flow velocity were also measured. In one case the transcutaneous technique was used to measure flow velocity with the transcutaneous probe placed over the external jugular vein in the supraclavicular area using the previously described technique.[11]

The flowmeter audio signal was continuously monitored by means of a loud speaker and recorded on tape. The analogue record of the flow velocity curves, intracardiac pressures, ECG, and phonocardiogram were recorded on a multichannel tape recorder (Sanborn, Model 3900) and on a light-beam oscillographic recorder (Electronics for Medicine, Model DR 12) operated at various paper speeds.

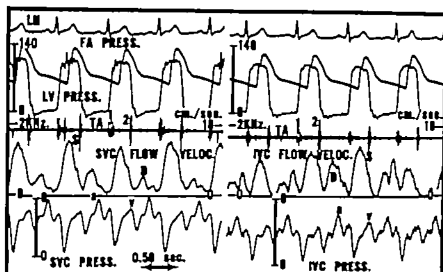


Fig 1 Lead II of the ECG femoral artery pressure (*FA*) left ventricular pressure (*LV*), phonocardiogram at the tricuspid area (*TA*) superior vena cava flow velocity (*SVC*) and superior vena cava pressure in a 26-year old man (Patient T Y) with normal heart and functional murmur Tracings on the left were made with the catheter tip located at the level of the SVC and the ones on the right at the level of the inferior vena cava (*IVC*). Note the essentially identical wave form on the flow velocity curves in these two areas of the venous circulation. The predominant wave of the flow velocity curve is the "S" wave occurring during ventricular systole.

A second catheter was introduced into another arm vein and advanced to the RA or SVC for the purpose of obtaining pressures. The tip of this catheter was located at the vicinity of the flowmeter catheter to obtain flow velocity and pressure simultaneously from the same site

Results

Group 1 RA and SVC flow velocity in normal subjects There were no significant differences in the wave form of the flow velocity curves recorded at the SVC or RA therefore these wave forms will not be described separately The flow velocity in these areas was *phasic* and *continuous* throughout the cardiac cycle Although some variation in the wave form occurred with regularity a definite *pulsatile* pattern could be identified in all cases (Fig 1) Two distinct waves were present in all normal subjects a third wave occurring during atrial systole was inconsistently present.

S WAVE This was the predominant wave of the flow velocity curves in the RA and SVC The onset of this wave followed the QRS complex of the ECG by 10 to 20 msec. it had a rapid rise and a round peak Its frequency shift ranged from 0 to 6 KHz. (kilohertz) corresponding to a calculated velocity of 0 to 54 cm per second The peak of this wave occurred in mid or late ventricular systole during the ascending limb of the T wave of the ECG and preceded the second heart sound of the phonocardiogram by 80 to 120 msec.

D WAVE. This wave was inscribed during ventricular diastole and its amplitude wave was approximately one third of the preceding "S" wave. The upstroke of the "D" wave occurred at the peak of the "v" wave of the RA pressure and coincided with the "y" descent.

A WAVE The "A" wave of the flow velocity curve was small and inconsistently present it was recorded in only one half of the normal subjects. In the majority of cases this wave was characterized by simple notch in the ascending limb of the following "S" wave Its peak occurred in the beginning of the descent of the "a" wave of the RA pressure curve, and it terminated prior to the onset of the QRS complex of the ECG The peak was round and approximately one fourth to one fifth of the amplitude of the "S" wave

Group 2 RA and SVC flow velocity in patients with tricuspid insufficiency

S WAVE The peak velocity of the "S" wave was significantly decreased as compared with normal subjects (Figs. 2 through 4) In the group with atrial fibrillation the peak flow velocity of the "S" wave varied from cycle to cycle—the shorter the cycle

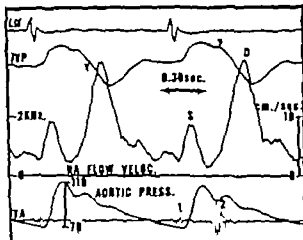


Fig. 2. Lead II of the ECG indirect jugular venous pulse (*JVP*) right atrial (*RA*) flow velocity aortic pressure, and phonocardiogram at the tricuspid area (*TA*) in a 39-year-old man (Patient A. G.) with tricuspid insufficiency and mitral valve prosthesis. The contour of the jugular venous tracing demonstrates sustained systolic wave, tall v wave and rapid "y" descent of the type seen in patients with tricuspid insufficiency. The flow velocity curve shows small "S" wave and large "D" wave; the peak of the D wave coincides with the downslope of the "y" descent.

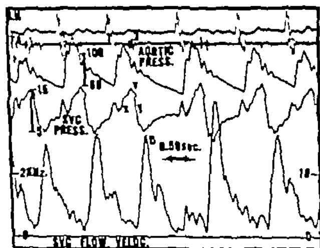


Fig. 3. Lead II of the ECG phonocardiogram at the tricuspid area (*TA*) aortic pressure, superior vena cava pressure (*SVC*), and SVC-flow velocity in a 46-year-old woman (Patient M. M.) with mitral stenosis and tricuspid insufficiency. Note dominant "S" wave with large "D" wave in the flow velocity curves occurring at the time of the downslope of the y descent in the SVC pressure. In addition, observe the variations in the beat-to-beat *peak flow* velocity in the SVC records which are related to the cycle length.

length of the preceding beat the smaller the peak flow velocity of the S wave. In the 3 patients with sinus rhythm the peak velocity of the "S" wave was regular varying only during respiration. The peak flow velocity of the "S" wave was *inversely* proportional to the amplitude of the D wave and in 5 patients the S wave had a peak velocity identical to the D wave.

The amplitude of the S wave was inversely proportional to the systolic regurgitant wave of the RA pressure ("x" descent). The S wave in patients with tricuspid insufficiency had an earlier peak

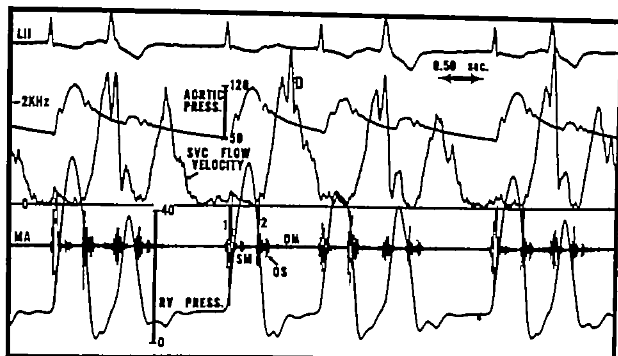


Fig 4 Lead II of the ECG aortic pressure superior vena cava flow velocity (*SVC*), the phonocardiogram at the mitral area (*M 1*) and right ventricular (*RV*) pressure in a 54-year-old woman (Patient A. K.) with mitral stenosis and insufficiency and tricuspid insufficiency the rhythm is atrial fibrillation with aberrantly conducted beats. Note the variation in beat to-beat peak flow velocity however the predominant wave of the SVC flow velocity record occurs during ventricular diastole (D waves).

(as compared with normal subjects) and began to descend in the early part of ventricular systole at the time of the rising pressure in the RA

D WAVE The most important abnormality in the wave form of the flow velocity tracing in patients with tricuspid insufficiency was the marked increase in the amplitude of the D wave In 12 of the 15 patients, the D wave was the only demonstrable wave of the flow velocity record (Fig 3) its peak velocity was inversely proportional to the S wave In patients with atrial fibrillation the peak velocity of the D wave varied from cycle to cycle and was directly proportional to the diastolic cycle length The upstroke of the D wave occurred shortly after the pulmonic component of the second heart sound of the phonocardiogram and at the time of the opening snap of the mitral valve it also followed the dicrotic notch of the aortic or pulmonary artery pressure (Fig 4) The peak of the D wave occurred during the downslope of the y descent of the RA pressure i.e at the maximal decline in the RA pressure The faster the heart rate was, the smaller the peak velocity of the D wave and the greater were the variations in its relationship to the S wave These findings also correlated well with the variations in peak pressure in the right ventricle and in the pulmonary artery pressure

In one case flow velocities in the ascending aorta and SVC were recorded simultaneously (Fig 5) The tracings demonstrated quite clearly that the D wave was large and diastolic in timing its amplitude was inversely proportional to the peak velocity of the aortic curves.

In 3 patients measurements of the inferior vena cava and hepatic vein flow velocities were made with the catheter tip located near the entrance of the vessel in the inferior vena cava The flow velocity wave form in these areas was essentially similar to the one described for the SVC and RA The same findings were also found in the transcutaneous measurement of jugular vein flow velocity (Fig 6)

A WAVE In this group there were only 3 patients with sinus rhythm In these cases the A wave was small and represented by a simple notch in the ascending limb of the S wave

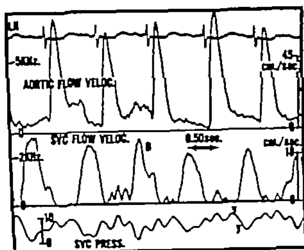


Fig 5 Lead II of the ECG, aortic flow velocity, superior vena cava flow velocity (SVC), and superior vena cava pressure recorded simultaneously in a 62 year-old woman (Patient S. H.) with mitral stenosis and tricuspid insufficiency Note large "D" wave in the SVC flow velocity record which is clearly diastolic in timing

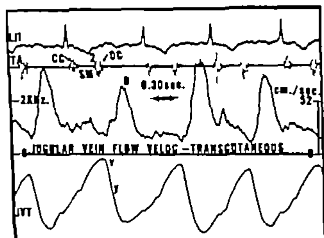


Fig 6. Lead II of the ECG phonocardiogram at the tricuspid area (*TA*), transcutaneous jugular vein flow velocity and indirect jugular venous tracing (*JVT*) in a 61 year-old woman (Patient H. W.) with mitral valve prosthesis and tricuspid insufficiency Note large "D" wave occurring during the y descent of the JVT *CC* Closing click *OC* opening click of the mitral valve prosthesis.

There was a gross correlation between the severity of tricuspid insufficiency as seen on the right ventricular angiogram and the amplitude of the D wave of the flow velocity records the largest D wave was found in patients with a severe degree of tricuspid insufficiency

RESPIRATION Inspiration resulted in a 20 to 30 per cent increase in peak velocity of the D wave, as shown in Fig 7 the peak amplitude of the S wave decreased proportionally

Group 3 RA and SVC flow velocity in patients with cardiac arrhythmias Transient episodes of tricuspid insufficiency were thought to have occurred in patients with a variety of cardiac arrhythmias.[3] In patients with atrial extrasystoles and in patients with heart block, if atrial contraction occurred at a time when the tricuspid valve was still closed the "S" wave was small and the D wave was large (Fig 8)

When several extrasystoles occurred in sequence, the velocity tracings became

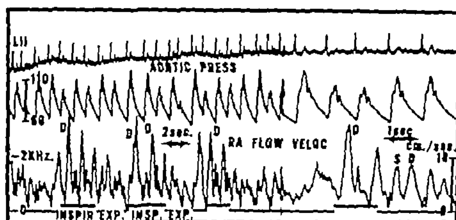


Fig 7 Lead II of the ECG aortic pressure, and right atrium flow velocity in a 54-year-old woman (Patient N. B) with mitral stenosis and tricuspid insufficiency the rhythm is atrial fibrillation. The influence of respiration on RA flow velocity is shown note that the D waves become exaggerated during inspiration.

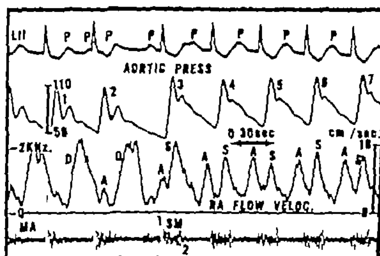


Fig 8 Lead II of the ECG aortic pressure, right atrium (*RA*) flow velocity and phonocardiogram at the mitral area (*MA*) in a 37 year-old woman (Patient D B) with mitral insufficiency the rhythm is atrial dissociation by interference. In beats 1 and 2 atrial contraction occurs during ventricular systole and results in a large D wave in beats 3 4, 5 6 and 7 the P R interval is essentially constant. Note that the flow velocity pattern changes significantly as compared with beats 1 and 2 A large A and S wa e are now present the "A wave is large because of a prolonged P R interval

monophasic with a single wave occurring during ventricular systole. The same find ings were observed during ventricular ex trasystoles.

In patients with complete heart block tricuspid insufficiency may also have oc curred when the P wave was inscribed during ventricular systole In these pa tients, it was possible to recognize a distinct pattern consisting of variations in the amplitude of the S wave and D waves as a function of the P R interval (Fig 8) Therefore the morphology of the flow velocity record during these arrhythmias was essentially similar to the ones described in Group 2 with tricuspid insufficiency

Discussion

The wave form of the flow velocity rec ords recorded in the RA and SVC in nor mal subjects was similar to the ones re corded with the electromagnetic-flowmeter system as described by Pinkerson [19] Wex ler [20] Mills [21] and their associates.

Phasic flow velocity measurements in patients with tricuspid insufficiency has not been reported It is well known that patients with tricuspid insufficiency have

sustained an elevated RA pressure (obliterated "x" descent) during ventricular systole secondary to incomplete closure of the tricuspid valve. Regurgitant flow therefore, occurs during ventricular systole and is the responsible factor for the presence of the systolic murmur described in this condition.

The abnormality of the wave form of the flow-velocity record in RA and SVC indicated that the velocity of flow decreased during ventricular systole (small S wave) with a compensatory acceleration occurring during ventricular diastole (large D wave); this pattern was opposite to that of the normal subjects. The decrease in flow velocity in the SVC and RA during ventricular systole coincided with a rising pressure in the RA and confirmed previous observation of the inverse relationship between pressure and flow in the RA.[22, 23] The decrease in the SVC flow during ventricular systole was most likely secondary to the presence of two opposite streams of blood occurring during that phase of the cardiac cycle: first, the regurgitant stream from the right ventricle to the RA and SVC; second, from the SVC toward the RA. Accumulation of blood in the RA, cava and other venous reservoirs resulted in acceleration of the flow toward the right ventricle during the following ventricular diastole.

This compensatory mechanism has been thought to be responsible for the large right ventricular end-diastolic volume observed cineangiographically and the presence of mid-diastolic murmur frequently heard in these patients.[3] This diastolic acceleration of flow during diastole was also recorded in the inferior vena cava, hepatic vein, and jugular vein (Fig. 6) confirming the well known clinical findings of a pulsatile liver and distended jugular vein observed in this condition.

The alterations in the wave form of the RA flow velocity curve in patients with tricuspid insufficiency (Group 2) cannot be attributed to the presence of atrial fibrillation alone.[26] Thirteen patients with idiopathic atrial fibrillation without evidence of tricuspid insufficiency and without demonstrable evidence of heart disease have been studied with this technique and they did not demonstrate the abnormalities of the velocity wave form described above. The findings observed during temporary episodes of cardiac arrhythmias also confirmed that which has been described above. In these patients, extrasystoles occurring at a time when the tricuspid valve was still closed caused a large increase in the amplitude of the "D" wave suggesting that tricuspid insufficiency occurred during that period of time.

The limitations of this technique have been previously described and related to the position of the catheter tip and to the fact that the Doppler flowmeter used in this report did not recognize direction of flow. In addition this technique was not quantitative since the angle that the tip of the catheter made with blood flow axis was unknown and the diameter of the chamber or blood vessel was unknown.

The advantage of this technique was that it provided measurement of flow velocity with a high frequency response and that the sensing devices did not have to be calibrated individually since they were calibrated by the Doppler equation instead. The electromagnetic flowmeter sensing devices need to be calibrated individually.[1-11] Other advantages of this approach included telemetry of blood flow velocity could be accomplished easily, thoracotomy for vessel exposure was not required, and vessels or cardiac chambers not directly amenable to transcutaneous examination could be explored. Multiple and repeated records at various levels in the right heart and large veins could be easily accomplished with this technique.

Summary and conclusions

Flow velocity records were obtained in the superior vena cava and right atrium in 52 patients using the Doppler catheter ultrasonic flowmeter telemetry system. The flow-velocity curves were recorded simultaneously with right and left heart pressures, phonocardiogram, and ECG. The pattern of flow-velocity curves in normal subjects was described, and consisted of a major "S" wave occurring during ventricular systole and a smaller "D" wave during ventricular diastole. There was an inverse relationship between flow velocity and pressures in the SVC and RA.

The major abnormalities observed in

patients with permanent tricuspid insufficiency consisted of a diminished S wave and a large increase in the diastolic D wave The A wave remained essentially unchanged These abnormalities reflected decreased flow velocity in the superior vena cava and right atrium during ventricular systole because of a high venous pressure due to regurgitation Compensatory acceleration of flow during ventricular diastole was probably the factor responsible for the high peak velocity of the diastolic D wave These findings were also present in the inferior vena cava hepatic vein and jugular vein velocity tracings Inspiration resulted in a significant increase in the amplitude of the D wave suggesting that regurgitant flow might have increased during that phase of the cardiac cycle.

It is concluded that this technique is suitable to study instantaneous phasic superior vena cava and right atrial flow velocity in conscious unanesthetized subjects with tricuspid insufficiency

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Acute coronary occlusion and the "power failure" syndrome

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The view that acute coronary artery occlusion is the cause of myocardial infarction is an oversimplification and is demonstrably incorrect in a certain per cent of cases.[1] For example Ehrlich and Shinohara reported that only 50 per cent of 38 patients with an acute myocardial infarct had an anatomically demonstrable acute coronary artery thrombosis. However they found that their cases could be divided on anatomic grounds into unicentric or multicentric infarcts 17 of 19 patients with unicentric infarcts had recent coronary artery thrombosis, whereas coronary thrombosis occurred in only 2 of 19 patients with multicentric infarcts. Similarly Miller Burchell and Edwards found an acute coronary artery occlusion in only 66 per cent of 94 patients with myocardial infarction. When their cases were subdivided into transmural or subendocardial categories, a high incidence of acute coronary occlusion was found with the transmural type of infarct and a low incidence with the subendocardial type.

The present study was initiated with the expectation that a similar division of cases could be achieved on the basis of the patients clinical course. With this in mind we studied 37 carefully selected patients with acute myocardial infarction and attempted to find differentiating features in the clinical histories of those patients with and those without acute coronary artery occlusion.

Methods

I. Initial study. Out of 256 patients studied by postmortem coronary arteriographic technique 56 were selected because of the presence of acute myocardial infarction. Out of the 56 cases we excluded those with a clinical course complicated by other major medical problems, since this combination made the role of the infarct in the clinical course impossible to evaluate. Table I is a compilation of the coexisting conditions which served as a basis for exclusion from this study. Using these criteria 41 cases were excluded leaving 15 cases in the initial study group. These cases were studied in the following manner

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1 PATHOLOGICAL STUDY Postmortem coronary arteriograms were done using a barium sulfate gelatin mixture as previously described[8] The right and left coronary arteries were cannulated separately and infused with differently colored mixtures allowing identification of antegrade and retrograde filling After formalin fixation the coronary arteries were cross-cut at about 4 mm intervals. Decalcification was used when necessary and multiple and occasionally serial sections of coronary artery lesions were made Multiple sections of the myocardium were taken and were stained with hematoxylin and eosin and when appropriate with Masson s trichrome stain.

2 CLINICAL STUDY The clinical records were examined by a member of the study group and by an independent observer entirely unfamiliar with the pathologic data and the cases were diagnosed as having power failure and no power failure (described below)

3 CORRELATION These cases were divided on the basis of the presence or absence of acute coronary occlusion (see Tables II and Table III) The two groups were then compared as to their clinical and pathologic features.

Table I Reasons for exclusion (41 cases)

Clinical findings	No of cases
Serious arrhythmia of hemodynamic significance	
Recurrent ventricular fibrillation	2
Recurrent ventricular tachycardia	1
Complete heart block	3
Cerebral or brain-stem infarction	5
Arsenic poisoning	1
GI hemorrhage	1
Severe metabolic disturbance (CO_2 narcosis, DT's, hyperkalemia, uremia)	4
Septicemia or severe infection	3
Dissecting aneurysm	1
Adrenal hemorrhage	1
Pulmonary embolization or infarction	4
Rupture of LV or IV septum	4
Surgical stress	6
Sudden unobserved death	6
Incomplete clinical or pathologic data	2
Total	44

II *Predictive study* Using the criteria suggested in the analysis of the initial group a second group of 2? cases of acute myocardial infarction was selected from approximately 71 patients with acute myocardial infarction These cases were evaluated clinically by two observers using the criteria for power failure (described below) and a prediction was made as to the presence or absence of acute occlusion. The clinical prediction was made in advance of any pathologic examination and the pathologic examination was made without the benefit of the clinical data. Pathologic study of this group of cases was performed in an identical manner to the initial group except that postmortem angiograms were not done The data were then correlated on the basis of the clinical diagnosis of power failure and the prediction of acute coronary occlusion (see Tables IV and V) The purpose of the predictive study was twofold (1) to add more data to the original observations and (2) to test the predictability of acute coronary artery occlusion using our criteria of power failure

Results

I *Initial study* The cases are divided on the basis of the pathologic diagnosis of acute occlusion (Table II) or no acute occlusion (Table III) In the acute occlusion cases (Table II) 2 of the occlusions were due to thrombi (one was a thromboembolus) 3 were due to both thrombi and intramural hemorrhage and 3 were due to intramural hemorrhage alone The ages of the patients history of previous myocardial infarctions sizes and locations of infarcts, and degrees of old atherosclerosis were almost identical in the two groups More complete analysis of each patient s clinical course revealed that 7 of 8 who were in the acute occlusion group showed a syndrome of power failure

The power failure syndrome is essentially a form of cardiogenic shock but is defined more strictly so as to exclude various conditions that may contribute to the shock picture (e g acidosis decreased effective blood volume and reflex vasodilatation) but which are not specifically caused by decreased contractility of the left ventricle The power failure syndrome is due to an acute myoca[illegible] that

Table II. Initial study: pathologic diagnosis: acute coronary artery occlusion

Clinical features					Anatomic findings							
					Coronary atherosclerosis†			Recent occlusion			Acute infarction	
Autopsy No.	Age, sex/race	Power failure	Onset to death*	Previous MI	RC	LAD	LC	Site	Prev. atherosclerosis‡ (%)	Mechanism	Size	Location
66-203	68, M C	Yes	5 days	Yes	0	3+	2+	LAD	60	Thrombus and IMH	Moderate	Ant. LV and IVS transmural
66-63	62, F N	Yes	5 days	No	3+	2+	0	RC	90	IMH	Moderate	Post. LV and IVS transmural
62-261	76, M C	Yes	8 hr	No	0	4+	2+	LAD	75	Thrombus and IMH	0	Too early for path. changes
63-342	61, M C	Yes	5 days	No	2+	4+	2+	RC	60	Thrombus	Moderate	Post. LV IVS transmural
285-64	55, M C	Yes	8 hr	Yes	3+	3+	2+	LAD	63	Thrombus and IMH	0	Too early for path. changes
64-60	48, M C	Yes	8 hr	Yes	3+	3+	2+	RC	60	IMH	Moderate	Ant. LV Lat. LV transmural
66-167	44, M C	Yes	36 hr	No	0	0	0	LAD	0	Embolus	Moderate	Ant. LV and IVS transmural
62-423	63, M C	No	24 hr	Yes	3+	3+	2+	LAD	90	IMH	Moderate	Ant. LV and IVS transmural

Abbreviations: M = Male; F = female; C = Caucasian; N = Negro; IMH = intramural hemorrhage; IVS = interventricular septum; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; LV = left ventricle; MI = myocardial infarct; RC = right coronary artery.

*Onset to death column is measured from first symptom of infarction to death.

†Coronary atherosclerosis graded: 0 = 0 to 10% occlusion, + = 1 to 50% occlusion, 2+ = 50 to 75% occlusion, 3+ = 75 to 95% occlusion, 4+ = 95 to 100% occlusion.

‡Represents % narrowing caused by old coronary artery disease in the acutely occluded vessel.

Table III. Initial study: pathologic diagnosis: no acute coronary artery occlusion

Clinical features					Anatomic findings					
					Coronary atherosclerosis				Acute infarction	
Autopsy No.	Age, sex/race	Power failure	Onset to death	Previous MI	RC	LAD	LC	Recent occlusion	Size	Location
66-82	59, F C	No	14 days	Yes	3+	4+	0	0	Moderate	Post. LV transmural
66-201	64, M C	No	4 days	No	3+	3+	2+	0	Moderate	Ant. LV wall transmural
66-301	69, F C	No	7 days	Yes	4+	3+	3+	0	Moderate	Apical subendocardial
63-24	55, M C	No	7 days	Yes	3+	3+	3+	0	Small	Ant. IVS subendocardial and multifocal
65-270	54, M C	No	10 days	No	0 (aortic stenosis)	0	0	0	Small	Ant. LV subendocardial and multifocal
64-278	49, F N	Yes	3 hr	Yes	3+	4+	4+	0	0	Too early for path. changes
66-266	70, F C	Yes	39 hr	Yes	3+	4+	0	0	Large	Ant. and post. LV IVS transmural

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Septicemia or severe infection	1
Dissecting aneurysm	1
Adrenal hemorrhage	4
Pulmonary embolization or infarction	4
Rupture of LV or IV septum	6
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II Predictive study Using the criteria suggested in the analysis of the initial group a second group of 22 cases of acute myocardial infarction was selected from approximately 71 patients with acute myocardial infarction These cases were evaluated clinically by two observers using the criteria for power failure (described below) and a prediction was made as to the presence or absence of acute occlusion. The clinical prediction was made in advance of any pathologic examination and the pathologic examination was made without the benefit of the clinical data. Pathologic study of this group of cases was performed in an identical manner to the initial group except that postmortem angiograms were not done The data were then correlated on the basis of the clinical diagnosis of power failure and the prediction of acute coronary occlusion (see Tables IV and V) The purpose of the predictive study was twofold (1) to add more data to the original observations and (2) to test the predictability of acute coronary artery occlusion using our criteria of power failure

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Table V. Predictive study: clinical diagnosis not power failure

Clinical features					Anatomic findings							
					Coronary atherosclerosis			Recent occlusion			Acute infarction	
Autopsy No.	Age, sex/race	Power failure	Onset to death	Previous MI	RC	LAD	LC	Site	Previous athero-sclerosis	Mechanism	Size	Location
W67-23	77 F C	No	9 days	Yes	3+	3+	4+	0	—	0	Moderate	Post. LV transmural
W66-173	38, M C	No	12 hr	No	0	3+	3+	0		0	Moderate	Apex LV transmural
W67 26	35 M C	No	30 day	Yes	4+	4+	3+	0		0	Large	Ant. and post. transmural
W67-8	60, F C	No	15 day	Yes	3+	3+	3+	RC	57%	Thrombus and ISMH	Moderate	Post. and septal transmural
67-80	64, F C	No	12 day	Yes	4+	3+	3+	0		0	Moderate	Post. LV patchy
W67-148	50, M C	No	18 days	No	4+	3+	3+	RC	90%	Thrombus	Moderate	Post. LV transmural
W68-77	48, M C	No	25 days	Yes	4+	4+	3+	0	—	0	Moderate	Ant. septal apex transmural

For abbreviations, see legend to Table II.

results in an inability of the myocardium to maintain the level of cardiac output necessary for adequate organ perfusion. There is evidence of underperfusion of one or more organ systems, so that signs of cerebral ischemia (disorientation, seizures), mesenteric insufficiency (abdominal pain), renal failure (oliguria), or pulmonary insufficiency (cyanosis, decreased pO_2) are present. Blood pressure is low (below 90 mm. Hg systolic) and responds only transiently or not at all to infusion of vasopressor agents. Thus, the features necessary to make the diagnosis of power failure include (1) evidence of acute myocardial infarct (history, electrocardiogram, elevated serum enzyme levels), (2) clinical signs of shock (systolic blood pressure below 90 mm. Hg, tachycardia, signs of increased catecholamine output), (3) clinical evidence of underperfusion of at least one organ system, (4) blood pressure and organ perfusion inadequacy responding only transiently or not at all to treatment including the use of vasopressor agents. Death occurs in one to five days.

A typical case history exemplified patients with this syndrome.

Illustrative case. A 64-year-old Negro woman (66-83, Table II) with one-month history of angina pectoris, was admitted with severe chest pain, nausea, vomiting, and diarrhea. Electrocardiogram and serum enzyme levels were diagnostic of acute myocardial infarction and the blood pressure was 80/60 (previously 140/70). There was pulmonary congestion and disorientation. The patient was given Aramine intravenously with increase of blood pressure to 90/70. Digitalis, pressors, and oxygen were given. Despite this treatment she remained oliguric and hypotensive. Severe abdominal pain was attributed to mesenteric ischemia; bowel sounds were normal. On the fourth and fifth day the blood pressure gradually decreased, pulmonary edema appeared, and the patient died on the fifth day. Postmortem examination revealed recent transmural posteroseptal myocardial infarction. The right coronary artery was occluded by recent hemorrhage into subintimal plaque close to its point of origin.

Comment. This course is typical of the power failure syndrome. The patient had mental confusion, oliguria, evidence of splanchnic ischemia, and hypotension. She responded slightly and transiently to pressor agents, but they became ineffective and the cardiovascular system collapsed, ending in death.

In the group with no acute occlusion (Table III) there were seven patients, of

Table IV Predictive study clinical diagnosis power failure

Clinical features					Anatomic findings								
					Coronary atherosclerosis			Recent occlusion			Acute infarction	
Autopsy No	Age sex/race	Power failure	Onset to death	Previous MI	RC	LAD	LC	Site	Previous atherosclerosis (%)	Mechanism	Size	Location
V66-226	67 M C	Yes	2 days	Yes	0	3+	3+	LAD	75	Thrombus	Large	Ant. and Lat. LV transmural
67-25	76 M C	Yes	11 hr	Yes	3+	3+	0	RC	5	Thrombus and IMH	Moderate	Post. LV transmural
W66-148	52 M C	Yes	5 days	Yes	3+	4+	4+	RC	95	IMH	Moderate	Post. LV transmural
W67 30	69 M C	Yes	1 day	Yes	3+	3+	2+	LAD	85	Thrombus	Moderate	Apical transmural
V67-38	45 M C	Yes	2 hr	Yes	4+	4+	2+	LC	50	Thrombus	Moderate	Post. septum transmural
W67 21	72 F C	Yes	14 hr	Yes	3+	3+	2+	RC	50	Thrombus and IMH	Moderate	Post. LV transmural
W67-86	66 F C	Yes	3 days	No	4+	3+	4+	LC	75	IMH	Large	Apical transmural
W67 122	70 M C	Yes	12 hr	No	3+	2+	4+	RC	60	Thrombus and IMH	Large	Post. LV transmural
W67 133	59 M C	Yes	4 days	No	3+	3+	4+	RC	50	Thrombus and IMH	Large	Post. LV transmural
W67 124	83 I C	Yes	1½ days	No	4+	3+	3+	RC LC	98 10	Thrombus and IMH	Moderate	Post. LV transmural
W67-200	79 F C	Yes	7 days	Yes	3+	4+	3+	LAD	99	Thrombus	Moderate	Ant. LV transmural
W67-112	65 F C	Yes	3 days	No	3+	4+	3+	RC	90	Thrombus	Moderate	Post. LV transmural
68-89	57 M C	Yes	1 day	Yes	3+	3+	2+	RC	75	Thrombus	Large	Post. LV transmural
W68-87	76 F C	Yes	5 days	Yes	2+	4+	3+	LAD	50	IMH	Moderate	Ant. LV subendocardial
W68-84	67 M	Yes	4 days	Yes	4+	3+	2+	LAD	95	Thrombus	Large	Apical transmural

Table V. Predictive study: clinical diagnosis, not power failure

Clinical features					Anatomic findings							
					Coronary atherosclerosis			Recent occlusion			Acute infarction	
Autopsy no.	Age, sex, race	Power failure	Onset to death	Previous MI	RC	LAD	LC	Site	Previous atherosclerosis	Mechanism	Size	Location
WU-22	77, F, C	No	9 days	Yes	3+	3+	4+	0	—	0	Moderate	Post. LV transmural
W6-173	25, M, C	No	12 hr.	N	0	3+	3+	0	—	0	Moderate	Apex LV transmural
16-25	38, M, C	Y	20 days	Yes	4+	4+	3+	0		0	Large	Ant. and post. transmural
W63-4	68, F, C	No	15 days	Yes	3+	3+	3+	RC	97%	Thrombus and DAH	Moderate	Post. and septal transmural
63-80	41, F, C	No	12 days	Yes	4+	3+	3+	0	—	0	Moderate	Post. LV patchy
W63-148	88, M, C	Y	19 days	No	4+	3+	3+	RC	99%	Thrombus	Moderate	Post. LV transmural
W66-77	43, M, C	No	25 days	Yes	4+	4+	3+	0	—	0	Moderate	Ant. septal apex transmural

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In the group with no acute occlusion (Table III) there were seven patients, of

whom five had no evidence of power failure. A case history will serve to illustrate this group

Illustrative case. A 59-year-old Caucasian woman (66-82 Table III) with myocardial infarction two months previously was admitted with acute chest pain. Initial clinical and laboratory observations (electrocardiogram acute phase reactants, etc.) substantiated the diagnosis of acute myocardial infarction. Her hospital course was uncomplicated and without further chest pain. The patient had no hypotension, oliguria, dyspnea, or cerebral ischemia Minimal congestive heart failure as manifested by basilar lung râles and ventricular gallop disappeared with digitalization and thiazide diuresis. While continuing to improve the patient suddenly without outward signs of deterioration, had a cardiac arrest which failed to respond to prompt resuscitative efforts. Postmortem study revealed an acute posteroseptal infarction and moderately severe coronary arteriosclerosis, with no acute coronary artery occlusion.

Comment This patient did not show evidence of the power failure syndrome There were no signs of shock or of organ hypoperfusion The patient did well for 2 weeks but died suddenly

II Predictive study The patients in this part of the study were grouped according to whether or not the investigator interpreted the clinical findings to be diagnostic of the power failure syndrome Tables IV and V summarize the data in these 2 groups and show that the prediction of acute coronary occlusion was right in all 15 cases (Table IV) The acute occlusion was a thrombus in 7 cases, a thrombus and intramural hemorrhage in 5 and intramural hemorrhage alone in 3 cases In the cases without power failure the prediction that there would be no acute coronary occlusion was correct in 5 of the 7 cases. The power failure group had an average life span after infarct of 2 5 days as opposed to the no power failure group with an average life span of 16 days postinfarct. By combining data to include the 15 patients in the initial study and the 22 in the predictive study it is seen that of 24 cases with the power failure syndrome, 22 had acute occlusion and of 13 cases without the power failure syndrome 3 had acute occlusion (Table VI)

Table VI Summary of findings in combined groups Using chi square test the differences between the groups are found to be highly significant ($p < 0.001$)

Presence of occlusion	*With power failure*	*No power failure*
With acute occlusion	22	3
No acute occlusion	2	10

Discussion

It appears that the pathologic entity of acute coronary occlusion may have the power failure syndrome as its clinical counterpart This syndrome does not follow every acute occlusion but is found in a high percentage of such cases. Power failure develops early after occurrence of the infarction and is generally unresponsive to therapy whether it be pressor agents or other cardiotonic measures. There is usually hypotension probably on the basis of inadequate cardiac output but this is not an absolute criterion There is always evidence of inadequate blood flow to one or more of the major organ systems which is thought to be on a basis of the inability of the heart to perform as a pump The patients in the groups analyzed revealed varying target organ responses hypotension cerebral ischemia decreased renal output abdominal pain thought to be due to mesenteric ischemia and hypoxia from pulmonary ischemia Normally if the patient survived the first 24 to 72 hours without developing the power failure syndrome he was not likely to develop it unless he had a new infarction

As the data clearly show there are exceptions to this concept with cases having acute occlusion without the power failure syndrome and cases with no acute occlusion that do have the power failure syndrome. Many of the acute infarction cases are complicated by arrhythmias, conduction defects metabolic problems, or disease of other organ systems which make the response of the entire organism to one insult (acute occlusion) difficult to assess. The data thus seem to point to 3 general classes of patients (1) those in whom power failure is apparent and the correct prediction of acute occlusion can easily be made using these criteria (2) those patients

in whom the syndrome of power failure clearly does not occur and the prediction of no occlusion can quite easily be made and (3) a third group of patients with features of both groups that tend to be complicated in their clinical course and do not lend themselves easily to classification. The correct prediction of occlusion in this group is more difficult and fraught with a high degree of error. For the most part, the latter type of case was excluded from the present study (Table I).

The observations of Kurland and associates[2] are similar to ours. Their figures indicate that of 46 patients with shock due to an acute myocardial infarct 67 per cent had an acute coronary occlusion of 81 patients with acute myocardial infarcts without shock, only 48 per cent had an acute coronary occlusion. These differences are significant at the 0.05 level, using the chi-square test with Yates correction.

It is possible that the acute occlusive episodes could have followed the infarction rather than having been the cause. It has been shown that there is predisposition to thrombosis in patients with ischemic heart disease.[6-9] When this is added to the hypercoagulable state that has been demonstrated to occur in shock of various etiologies, the chances of coronary thrombosis occurring in patients with acute infarction plus power failure are enhanced. A similar conclusion was reached by Blumgart and associates,[10] who observed multiple coronary artery thrombosis in patients dying of shock caused by noncardiac conditions. This does not, however, explain the occlusions related to intramural hemorrhages.

Summary

Thirty-seven patients with acute myocardial infarction were studied post mortem. Twenty-five had acute coronary artery occlusion (thrombosis and/or intramural hemorrhage). 22 of these patients showed the clinical "power failure" syndrome (88 per cent). In contrast, only 2 out of 12 patients (17 per cent) who had no demonstrable acute coronary artery occlusion had evidence of power failure.

The authors are indebted to Dr. J. Gunter and the Watts Hospital Pathology Staff for their helpful assistance.

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Arterial oxygen tension in acute myocardial infarction

Serial analysis of clinical state and blood gas changes

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Development of specialized hospital units for management of patients with acute myocardial infarction has led to improved mortality and morbidity rates due to intensive treatment of arrhythmias. Attention is now being focused on the physiologic derangements which may complicate this disorder Arterial hypoxemia has been documented in myocardial infarction recently [1-7] Reduced arterial oxygen tension has been attributed in part to increased physiologic dead space and ventilation perfusion abnormalities.[2-7] Shunting of blood with low oxygen tension into the pulmonary veins has been described in some patients with myocardial infarction but there is uncertainty about the contribution of this mechanism to hypoxemia.[2,3,4-7]

Both alkalosis[4] and acidosis[8] have been reported in myocardial infarction but most workers agree that pH and arterial carbon dioxide tension remain relatively normal [2,4] Changes in central venous oxyhemoglobin saturation may reflect clinical severity in cardiac infarction[9] but these measurements are difficult to interpret since they may be influenced by a number of factors.

Previous reports of arterial hypoxemia[1-7] have included few serial observations. Correlation of arterial blood gas measurements with simultaneous evaluation of the clinical status has been lacking The present study was undertaken to obtain daily measurements of arterial oxygen and carbon dioxide tension pH and lactate concentration in patients with acute myocardial infarction and to relate these data with daily clinical estimation of the functional severity of the infarction

Materials and methods

Serial studies were performed during 40 episodes of acute myocardial infarction in 39 randomly selected patients admitted to a coronary care unit. A definite diagnosis of myocardial infarction based on previously defined criteria was established in each patient.[10] The average delay from onset of infarction to admission to the

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Table I Arterial blood gases in normal subjects and in patients without disease of the heart or lungs

Parameter	Breathing air	Breathing 28% O	ΔPaO_2
Ideal controls (n = 15)			
PaO (mm. Hg)	99 ± 6	139 ± 11	40 ± 10
SaO (%)	98 ± 1		
PaCO (mm. Hg)	40 ± 4	40 ± 4	
pH (units)	7 41 ± 0 02	7 41 ± 0 02	
Lactate (ml./dl.)	8 ± 3		
Age-matched controls (= 18)			
PaO_2 (mm. Hg)	87 ± 7	123 ± 12	36 ± 10
SaO_2 (%)	97 ± 1		
$PaCO_2$ (mm. Hg)	39 ± 3	40 ± 4	
pH (units)	7 42 ± 0 03	7 42 ± 0 03	
Lactate (ml./dl.)	8 ± 4		

*Mean ±1 standard deviation.

coronary care unit was 7 hours. Age of patients ranged from 40 to 80 years (mean 61.2) There were 32 men No patient had overt chronic pulmonary disease Ten patients died during hospitalization

The patients were examined by one of us at the time of each blood collection and grouped into one of four clinical classes I no congestive failure II moderate congestive failure (râles, gallop) III pulmonary edema and IV shock (systolic pressure below 90 mm Hg and signs of peripheral vasoconstriction)

Data were collected each morning for the first three or fou days after admission and at varying intervals during the remainder of hospitalization An arterial blood sample was drawn into an heparinized plastic syringe after the patient had been quietly breathing air for at least 15 minutes. An aliquot of blood was precipitated with 0 6 M of perchloric acid for subsequent lactate determination. Samples were immediately iced and blood gas analyses performed as rapidly as possible. The patient was then fitted with a plastic Venturi-type mask adjusted to deliver 28 per cent oxygen The concentration of inspired oxygen was monitored with a Servomex paramagnetic oxygen analyzer After 20 minutes a second arterial blood sample was drawn Blood gas analyses were performed with a Radiometer pH Meter 27 with Gas Monitor A Severinghaus glass electrode was used to measure carbon dioxide tension The polarographic oxygen electrode with a polypropylene membrane was routinely calibrated with air-equilibrated water At least once daily the calibration was checked with blood which had been equilibrated with air in a tonometer for 20 minutes. The pH electrode was calibrated with freshly opened ampules of buffer of pH 6.84 and 7.38 Oxyhemoglobin saturation was derived from pH and oxygen tension Lactate was estimated with the UV method of enzymatic assay

Care was observed in obtaining blood samples, i.e careful local anesthesia, use of sharp 20 gauge disposable needles and firm pressure for several minutes over the puncture site to prevent hematoma formation. With these precautions no complications were encountered and there was little difficulty in obtaining patients consent for repeated studies.

Table I shows data from two groups of control studies. "Ideal controls consisted of 15 healthy hospital personnel aged 18 to 40 years (mean 25 years) Age-matched controls were patients without symptomatic cardiopulmonary disease whose age and sex distribution were similar to that

*Servomex, Oxymeter Ltd., London, England.

*C. F. Boehringer & Soehne, GMBH, Mannheim, Germany.

Table II *Blood gas studies in myocardial infarction Distribution according to estimate of clinical severity*

Most severe clinical class	*No of patients*	*No. of observations in each class*			
		I	*II*	*III*	*IV*
I	8	27	—	—	—
II	18	21	60	—	—
III	7	7	17	8	—
IV	7	5	12	7	13
Total	40	60	89	15	13

*Total studies 177

Table III *Arterial oxygen tension and increment with 28 per cent oxygen arterial oxyhemoglobin saturation carbon dioxide tension pH and lactate concentration in patients with acute myocardial infarction*

Clinical class	*Parameter*	*Breathing air*	*Breathing 28% O*	*Δ PaO*
I	PaO_2 (mg Hg)	86 ± 10	116 ± 20	32 ± 13
	SaO (%)	97 ± 1	98 ± 1	
	PaCO (mm. Hg)	38 ± 5	36 ± 6	
	pH (units)	7 44 ± 0 05	7 46 ± 0 06	
	Lactate (mg /dl)	8 ± 2		
II	PaO_2 (mm. Hg)	71 ± 8	95 ± 17	24 ± 11
	SaO_2 (%)	95 ± 3	97 ± 2	
	PaCO (mm Hg)	39 ± 6	39 ± 6	
	pH (units)	7 43 ± 0 04	7 03 ± 0 04	
	Lactate (mg /dL)	10 ± 4		
III	PaO (mm. Hg)	60 ± 7	73 ± 10	12 ± 8
	SaO (%)	92 ± 5	95 ± 4	
	PaCO (mm. Hg)	38 ± 4	39 ± 4	
	pH (units)	7 42 ± 0 05	7 42 ± 0 06	
	Lactate (mg./dL)	17 ± 9		
IV	PaO (mm Hg)	57 ± 11	67 ± 11	10 ± 6
	SaO_2 (%)	89 ± 6	93 ± 5	
	PaCO (mm. Hg)	39 ± 6	40 ± 6	
	pH (units)	7 41 ± 0 04	7 39 ± 0 06	
	Lactate (mg /dl)	20 ± 8		

Mean ± 1 standard deviation.

of the study patients. As can be noted in Table I arterial oxygen tension during air breathing and during inspiration of 28 per cent oxygen was lower in the age-matched controls than in the ideal controls (p <0 005 for both) although the increments in tension induced by increased oxygen concentration were identical

Since repeated arterial punctures were necessary to obtain blood samples during the two different ventilatory states and the Venturi mask was applied to the patient after the resting sample had been obtained it could be argued that the experimental conditions influenced the results by inducing some degree of hyperventilation during the second portion of the study This possibility [illegible]

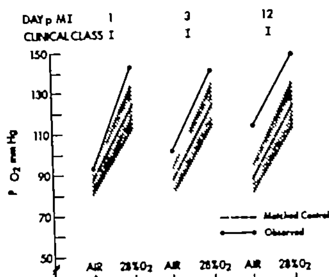


Fig. 1 Hypoxemia in myocardial infarction—no heart failure. Arterial oxygen tension while breathing air and 28 per cent oxygen in patient with uncomplicated myocardial infarction Note that oxygen tensions are normal in absence of heart failure. Closed circles depict observations in patient studied on first, third, and twelfth hospital days. In this and subsequent figures dashed line connects normal values, shaded area represents 1 standard deviation of age-matched control values

by comparing the change in arterial carbon dioxide tension from air to oxygen inhalation in each clinical class. Thus, mean CO_2 tension (mm. Hg) changed as follows Class I −1 64 (range +5 to −8) Class II −1 1 (+5 to −11) Class III −0 65 (+6 to −4) Class IV +0.81 (+8 to −5) These differences are not statistically significant. We conclude therefore that alveolar ventilation remained essentially unchanged during the experimental study

Results

Since each patient was studied several times during hospitalization often during different clinical states the data were analyzed according to the clinical class at the time of study Table II depicts the distribution of 177 studies according to clinical class at the time of sampling and also indicates the distribution of patients grouped according to their worst clinical class. Blood gas, pH and lactate data grouped according to clinical class are shown in Table III

No heart failure, Class I Sixty observations were obtained in the absence of clinical signs of congestive failure. Mean arterial oxygen tension was 86±10 mm. Hg when the patients were breathing air and 116±20 mm. Hg during inhalation of 28 per cent oxygen These data are not significantly different from that of the age-matched control population However when the observations are separated into two groups divided according to the presence or absence of heart failure previously during the illness significant differences were apparent. Mean arterial oxygen tension of 27 observations in 8 patients who remained in Class I throughout hospitalization averaged 89±9 mm. Hg compared to value of 83±10 mm. Hg ($p<0.05$) for 33 measurements in 18 patients who had been in heart failure previously but who were in Class I at time of study Thus, patients who recovered from heart failure had slightly lower resting arterial oxygen tension than patients who never developed clinical failure. The increment with 28 per cent oxygen did not differ in these subgroups.

Fig 1 illustrates serial measurements from a patient in whom congestive failure was never detected clinically Note that on the first, third and twelfth days after acute myocardial infarction arterial oxygen tensions and the increment with 28 per cent oxygen were normal

Moderate heart failure Class II Eighteen patients with clinically recognized congestive failure had 60 studies while in failure

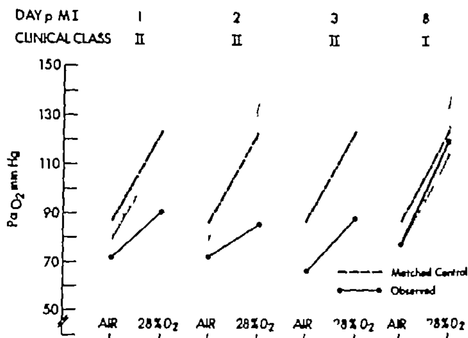


Fig 2 Arterial oxygen tension while breathing air and 28 per cent oxygen in a patient with myocardial infarction complicated by moderate congestive heart failure. Oxygen tensions are depressed during first three days of illness while heart failure is present. Following recovery arterial oxygen tensions are normal

and 21 observations after recovery The mean arterial oxygen tension of 71±8 mm Hg when breathing air and the increase to 95±17 mm Hg with oxygen breathing in Class II was significantly lower than the values in Class I ($p<0.001$ for both) As mentioned above when failure was no longer detected clinically oxygen tension remained lower in patients who had been in Class II than in those who remained in Class I throughout hospitalization Three Class II patients continued to have decreased oxygen tension throughout recovery and ambulation despite disappearance of clinical failure In the other 15 patients, however arterial oxygen tension eventually rose to normal after recovery from failure Although oxygen tension was reduced in Class II patients while they were breathing room air increment in inspired oxygen concentration to 28 per cent raised oxyhemoglobin saturation to more than 93 per cent in all but one instance.

Fig 2 depicts serial observations in a patient who was admitted in moderate failure but improved clinically after the third day Note that arterial oxygen tension was low and the increment with administration of 28 per cent oxygen was small until evidence of heart failure cleared. On the eighth day the data were normal.

Pulmonary edema and shock Classes III and IV Fifteen observations were obtained in ten patients in pulmonary edema. Thirteen studies were performed in seven patients during cardiogenic shock. Mean arterial oxygen tension in pulmonary edema during air breathing was 60±7 mm Hg During inhalation of 28 per cent oxygen the mean arterial oxygen tension increase was only 12±8 mm Hg Both values were significantly different from those observed in Class II ($p<0.001$)

In patients meeting the criteria for cardiogenic shock arterial oxygen tensions ranged from 30 to 71 mm Hg with a mean 57±11 mm Hg values significantly lower than data from control and Classes I and II patients ($p<0.001$) The incremental response to 28 per cent oxygen was 10±6 mm Hg Overt pulmonary edema was clinically present in 4 of the 7 patients with cardiogenic shock Mean arterial oxygen tension values in Classes III and IV were not significantly different

Fig 3 depicts the clinical and laboratory data obtained in a 78 year-old man with acute myocardial infarction On the fifth hospital day he developed hypotension oliguria and complete heart block and was classified as being in car[...] shock

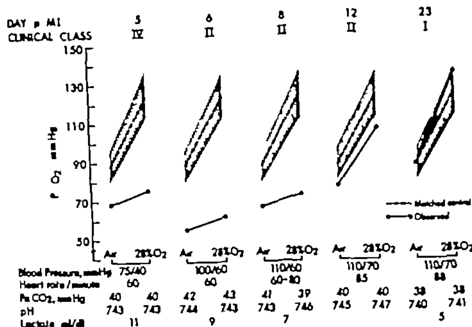


Fig. 3. Serial analyses of arterial oxygen tension during and after cardiogenic shock in patient with acute myocardial infarction. Oxygen tension correlates with the clinical state. Severe hypoxemia while the patient breathes room air and 28 per cent oxygen persists during shock and heart failure, Day 5 through Day 6. After recovery Day 23 data are normal. Note that $PaCO_2$, pH, and blood lactate are surprisingly normal during acute illness.

Arterial oxygen tension during air breathing was 68 mm. Hg and increased only 5 mm. Hg with oxygen breathing. Following endocardial pacing and norepinephrine infusion he gradually improved clinically. On the eighth hospital day arterial oxygen tension remained low but by Day 12 had returned toward normal. Studies on Day 23 were within normal limits. Arterial CO tension, pH and lactate measurements were within normal limits throughout.

Serial observations

Serial studies in patients who remained in Classes I and II during the first three days after infarction showed a slight tendency toward improvement in oxygen tension. Thus, in Class I arterial oxygen tension with the patient breathing air averaged 84±11 mm. Hg on Day 1 and 87±9 mm. Hg on Day 3. In Class II the values were 69 ±9 mm. Hg on Day 1 and 72±8 mm. Hg on Day 3.

As patients improved clinically arterial oxygen tension rose (Fig. 4). Thus in six patients in Classes III or IV who gradually recovered mean oxygen tension was 57 mm. Hg in Class IV (2 patients), 60 mm. Hg in Class III (5 patients), 67 mm. Hg in Class II and 85 mm. Hg in Class I. These serial observations confirm the relationship between clinical evaluation of cardiac function and arterial oxygen tension in myocardial infarction.

Other measurements

Arterial oxyhemoglobin saturation was normal in Class I and Class II but was significantly decreased ($p < 0.05$) in Class III and Class IV patients (Table III).

Arterial carbon dioxide tension and pH were both normal in all four classes, although individual values varied more widely than in the control population.

Arterial lactate increased with clinical severity. Mean values in Classes I and II were within normal limits, but rose significantly in Class III ($p < 0.01$) and Class IV ($p < 0.001$) (Table III).

Discussion

The present study in patients with myocardial infarction has demonstrated a relationship between arterial oxygen tension and functional severity as evaluated by clinical estimation of the presence and de

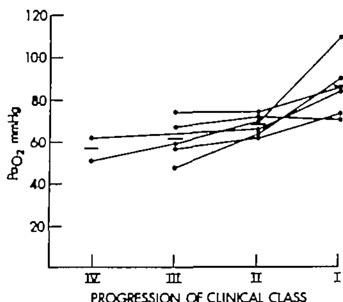


Fig. 4 Serial arterial oxygen tensions in patients breathing room air during recovery from complicated acute myocardial infarction. Progressive rise in oxygen tension parallels clinical improvement. In cardiogenic shock (Class IV) arterial oxygen tension is reduced. With pulmonary edema (Class III) and moderate heart failure (Class II) hypoxemia improves. After recovery from heart failure arterial oxygen tension is near normal level of 87 ± 7 mm. Hg

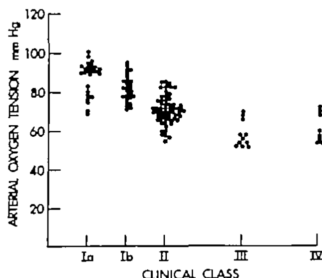


Fig 5 Arterial oxygen tensions in patients with acute myocardial infarction breathing room air Data are plotted according to clinical classification of functional severity of illness. Class *Ia*, no heart failure during illness Class *Ib*, recovery from heart failure Class *II* moderate heart failure Class *III* pulmonary edema; Class *IV* cardiogenic shock. Note correlation between clinical severity and degree of hypoxemia.

gree of left ventricular failure or shock The more severe the clinical evidence of failure, the lower the oxygen tension when the patient breathes air (Fig 5) Furthermore, the increment in arterial oxygen tension induced by a modest increase in oxygen concentration in the inspired air is inversely related to the clinical state. Thus the more severe the heart failure the less the increment. Although previous workers have reported hypoxemia in myocardial infarction the relationship between reduced oxygen tension and the functional severity of the illness has not been well documented McNicol and associates[3] observed that patients who died had the most severe hypoxemia but did not correlate findings in the less critically ill patients

Valentine and associates[9] noted a progressive decline in oxygen tension during the first three days after hospital admission in a group of patients with myocardial infarction. In contrast our patients with moderate or no failure actually had a slight rise in arterial oxygen tension after three days. The variation in results may possibly reflect differences in clinical usage of sedatives, diuretics, or digitalis.

Others [1-10] have noted a delay in return of oxygen tension to normal following clinical recovery In the present study patients who recovered from heart failure had slightly lower arterial oxygen tension than did patients who never developed failure. A few patients who recovered from moderate heart failure remained hypoxemic throughout hospitalization On the other hand the majority of our patients did achieve oxygen tensions nearly comparable to age-matched control values after recovery Thus, persistent hypoxemia in acute myocardial infarction is far from the rule after clinical improvement. If present it may reflect noncardiac influences.

The effectiveness of oxygen therapy was evaluated by administration of 28 per cent oxygen. This concentration is below the level associated with increased systolic pressure and reduced cardiac output in both normal subjects[13] and patients with myocardial infarction [14] The data indicate that moderate increase in oxygen concentration in the inspired air raises oxyhemoglobin saturation satisfactorily in patients with mild or moderate heart failure. In patients with pulmonary edema or shock, however more efficient means of oxygen delivery are required to produce adequate oxygenation. Our experience indicates, also that it is wise to monitor the adequacy of oxygenation in severely ill patients with myocardial infarction by appropriately timed analysis of arterial oxygen tension

Goldman and co-workers[9] recently reported that central venous oxygen measurements reflect the clinical state in acute myocardial infarction. Serial sampling from a central site requires an indwelling catheter which may predispose to phlebitis or infection. Interpretation of the findings may be difficult since reduction in central venous oxygen saturation may be due to either arterial hypoxemia, a decrease in cardiac output or a change in oxygen consumption. To obtain useful information for clinical management we prefer analysis of arterial oxygen tension. Arterial punctures are simple and safe to perform and the data provides clinically helpful information

Although arterial oxyhemoglobin saturation is directly related to blood oxygen content for a given blood hemoglobin content, it is useful to measure arterial oxygen tension In the range of values usually encountered in patients with hypoxemia complicating acute myocardial infarction the sigmoid relationship between oxygen tension and oxyhemoglobin saturation is such that relatively large changes in tension occur with small changes in saturation. Thus, changes in tension are a more sensitive indicator of clinical derangement than are those of oxyhemoglobin saturation.

A further reason for emphasizing arterial oxygen tension rather than oxyhemoglobin saturation lies in a consideration of the mechanism of oxygen transfer from blood to cell. Diffusion of oxygen from hemoglobin to mitochondria is dependent on a gradient of partial pressure Therefore, a high blood oxygen tension might in theory increase the effective diffusion gradient to areas hypoxic because of marginal blood supply and thus increase oxygen transfer preserving cell function. Although this argument supports the almost universal clinical use of oxygen in the early phase of acute myocardial infarction experimental observations are scant.[8]

Absence of hypocapnia in the patients studied during pulmonary edema was surprising since some degree of respiratory alkalosis might have been anticipated De pression of ventilation by sedatives or narcotics was probably not a factor since morphine was administered within two hours of sampling in only four of the fifteen patients studied in pulmonary edema and the data from these patients were indistinguishable from the remainder The relatively normal arterial carbon dioxide tension is most likely a reflection of the fact that it was not possible to obtain data during the fulminant phase of the pulmonary edema. All studies were obtained during a subacute stable phase when patient cooperation could be assured. Thus, hyperventilation was probably not present

and these blood gas data do not represent that which might be obtained in the most severely ill patient

The normal pH values were also unexpected since only two studies were done subsequent to bicarbonate administration Eleven patients had an initial pH of 7 37 or less but only three died Thus in contrast to a previous report[4] measurement of pH did not prove a useful indication of either the clinical state of the patient or his chance of survival

Lactate concentrations in the Class III and IV patients were increased Rise in blood lactate with increase of clinical severity has been noted by others.[1] In contrast to the report of Broder and Weil [12] we did not find blood lactate concentration a useful prognostic value Four of the five highest levels in our series were from patients who did eventually recover This fact together with the relatively cumbersome analytical method militates against blood lactate as a guide in evaluating either functional severity or clinical outcome

The mechanisms responsible for the arterial hypoxemia observed in acute myocardial infarction are not well defined There are several possible explanations The normal arterial carbon dioxide tension obtained in the present study and the increased ventilation measured by others[3, 7] suggest that hypoventilation does not play an important role. The contribution of abnormal ventilation perfusion relationships seems to vary from one studied population to another These disparate results may stem from technical variables such as the use of polarographic[17, 4] and paramagnetic methods of expired gas analysis and may also reflect problems inherent in comparing results among patients with varying degrees of clinical severity

Differences in analytical methods and patient selection make comparison of 100 per cent oxygen shunt measurements among various authors difficult. Preliminary studies in our laboratory suggest that such shunting is a significant contributor to hypoxemia especially in the more seriously ill patients. It is generally agreed that failure to attain arterial oxygen tensions of over 600 mm Hg while breathing 100 per cent oxygen indicates right to left shunting of blood [19] This shunting would include passage of blood through alveoli which are essentially unventilated through anatomic shunts and through alveoli filled with edema fluid The extent to which these factors combine to influence diffusion of oxygen from alveolar air to pulmonary capillary blood has not been fully determined although a preliminary report holds that in most patients diffusion is normal[4] It, therefore, seems reasonable to regard the mechanisms producing hypoxemia as uncertain until more precise evaluation of the relative contributions of pulmonary venous hypertension interstitial edema regional atelectasis and increase in alveolar fluid is available

It is important to note that in many instances the deranged pulmonary function is at least partially reversible by deep breathing[3, 4, 7] This observation would tend to implicate disturbed ventilation and collapse of lung units in the production of hypoxemia This would also seem to warn against overzealous use of sedatives and to have important implications for the nursing care of coronary patients.

The observation that inhalation of 28 per cent oxygen usually achieved adequate oxyhemoglobin saturation suggests that the mask used in the present study may be useful in patients with chronic obstructive pulmonary disease complicated by an acute myocardial infarction Further observations in this type of patient are needed to evaluate this possibility

Summary

The arterial hypoxemia frequently present in acute myocardial infarction was compared with simultaneous clinical examination on 177 occasions throughout 40 episodes of infarction and recovery The arterial oxygen tension and the increment with 28 per cent oxygen were found to correlate with clinical severity. The daily arterial carbon dioxide pH and lactate studies did not accurately reflect changes in clinical course The complex physiologic derangements are discussed

Arterial blood gas analysis is a safe and useful tool for evaluating the clinical course and management of acute myocardial infarction

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Experimental and laboratory reports

Significant determinants of successful reversion of fibrillation by a new DC defibrillator

An experimental study

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Since the appearance of Lown's[1] publication many workers have observed the more consistent defibrillatory effectiveness greater safety and less frequent incidence of ventricular fibrillation associated with the use of DC as well as single-cycle square-wave AC discharges as compared to AC countershock[2-6] Detmer and associates[7] and Peleska[4] have carefully delineated the ranges of optimally effective DC defibrillatory wave form amplitude and duration as well as ineffective and unsafe defibrillation wave-form parameters in terms of the capacitor and inductor storage elements The introduction of a new DC defibrillator* utilizing multiple capacitor inductor sections (delay line) has made available an instrument with a unique effective safe capacitor discharge wave form similar to that described by Balagot and associates.[8] Because of the multiple storage elements it is advantageous to express the defibrillatory efficacy in terms of energy (joules or more commonly watt seconds)

There are several potential avenues for energy losses in experimental or clinical situations wherein defibrillators are employed for countershock Such losses may be enumerated as follows

1 Internal losses in the defibrillator delay line (a) Losses within the series voltage dividing circuit comprised of patient resistance and the resistance of the inductor(s) windings in the delay line (in some instances 16 to 20 ohms effective) (b) losses associated with the mismatching of the load impedance and the characteristic impedance of the delay line. If the output electrodes of such a delay line are connected to a patient load whose impedance is equal to the characteristic impedance of the line the line and its termination are said to be matched Under these conditions all the energy transmitted down the line is absorbed by the load except as stated in *a* If the output terminals of a line are connected to a patient load whose impedance is anything other than the characteristic impedance of the line the line and its termination are said to be mismatched A portion of the energy

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*Monopulse 807 (United States Patent 3,258,013) Manufactured by Zenith Radio Corporation, Chicago, Ill., and marketed by Travenol Laboratories, Inc., Morton Grove, Ill.

transmitted down the line under these conditions is not absorbed by the patient but is reflected back into the delay line which has a finite resistance.*

2. Losses via shunt pathways in the patient or animal load. (a) Losses via the ECG grounded input lead to an electrocardiograph or oscillograph. (b) possible shunt losses via ECG input leads associated with normal breakdown to ground of protective elements in these instruments in the face of the high voltages encountered during countershock. (c) losses to any other instruments or earth ground to which an animal or patient may be connected.

These possible avenues for energy losses necessitate determination of *delivered* effective interelectrode energies rather than *stored* energies in the design of experiments to define optimal defibrillation conditions, defibrillation thresholds, and tissue resistances. Accordingly, an acute awareness not only of the magnitude of stored energy but also of the fractional portion of this energy delivered *through the tissue load* is of utmost importance. The present report describes the results of experimental canine studies in which electrode size, defibrillation mode, tissue resistance, body size, and heart size were investigated as determinants of delivered "effective" threshold defibrillation energies. Losses by shunt pathways will be the subject of another publication.

Materials and methods

Animal preparation and procedures. Using a Monopulse 807 DC defibrillator similar to that described by Balagot and associates defibrillation threshold and tissue resistance studies were carried out in mongrel dogs weighing from 3 to 27 kilograms. This defibrillator provides an underdamped DC pulse with a maximal amplitude of about 1,600 volts (loaded) and a half-amplitude duration of 7 to 8 msec. All animals were anesthetized with 30 mg. per kilogram of pentobarbital sodium administered intravenously. Supplemental intravenous doses of 3 mg. per kilogram of this barbiturate were readministered as required to maintain a uniform level of anesthesia.

In *all* cases ventricular fibrillation was induced by application of *single* 2 to 4 second bursts of AC current. For external fibrillation a 60 c.p.s. 360 volt R.M.S.** (open circuit) AC stimulating voltage applied through an internal current limiting 3 K resistor was delivered transthoracically via circular plate electrodes 9 cm. in diameter for a period of 2 to 4 seconds. Good electrode contact was assured by application of saline-soaked 100 sq. cm. gauze pads sutured to the clipped skin of the lateral thoracic walls. Internal fibrillation was accomplished by application of AC current directly to the exposed ventricular myocardium; the stimulus parameters were 60 c.p.s., 6.3 volt R.M.S. applied for 2 to 3 seconds until fibrillation ensued. Ventricular fibrillation was allowed to continue for a period of 15 seconds in all fibrillation-defibrillation sequences. Cardiac status was ascertained by visual observation of the heart in the open-chest procedures, by monitoring femoral arterial blood pressure via a Statham strain-gauge transducer and Grass oscillograph, and/or the ECG displayed on the cardioscope module of the delay line defibrillator. Gross anatomic alterations resulting from repeated fibrillations with the equipment and energies described have not been observed.

Thresholds were determined for external defibrillation modes I and II (Table I) by a sequential discharge of 200, 160, 120, 80, 60, 40, 20, 10, 5, or 1 W-S of *stored* (meter indicated) energy in this order. Fibrillation was produced at 2 minute intervals, until such discharge failed to defibrillate on the first shock, at that time a 200 W-S shock was immediately applied to provide rapid reversion to sinus rhythm. The thresholds for internal defibrillation modes III to VI inclusive (Table I) were determined by countershocking sequentially at 40, 20, 10, 5, and 1 W-S until a discharge failed to defibrillate on the first shock, at which time a 40 W-S shock was applied to re-establish sinus rhythm. In both cases, defibrillation threshold is defined here as the lowest delivered "effective" energy in the sequence

*$W = \frac{1}{2}CV^2$, where W = total energy stored in the capacitor(s) in watt seconds (W-S), C = capacitance in farads, and V = the initial DC charge on the capacitor in volts.

**R.M.S. = root-mean-square.

Table I Mean defibrillation thresholds and interelectrode resistance in dogs

Defibrillation mode	Heart weight range (mean) (Gm.)	Body weight range (mean) (Kg.)	Mean delivered effective threshold energy ± S.E.M (W S)	Mean interelectrode resistance ± S.E.M (ohms)	No. of dogs
External	35- 99(68)	4 1 14 7(8.6)	30 ± 3.25	70 ± 3 25	39
Bilateral	100-163(128)	11 1 25 0(15 7)	40 ± 4 77	77 ± 5 41	18
	164 277(173)	11.3-27 6(21 8)	49 ± 8.14	74 ± 7 09	12
External	35 99(73)	5 6- 9 8(7 8)	32 ± 10.54	95 ± 10.53	3
Anterior posterior	100-163(132)	11 2 19 0(14 6)	50 ± 12 41	105 ± 5 74	5
	164-227(197)	19 7 25 0(22 7)	75 ± 13 10*	97 ± 10 19	5
Internal	100-150(123)	11.2 19 0(15 8)	7 ± 2.34	98 ± 4.36	3
External	150-227(197)	19 7 24.3(22 1)	10 ± 2 66	66 ± 11.25	5
Internal	100-150(131)	11 2 25 0(17 4)	2 ± 2 24	29 ± 3.06	10
Large paddles (10 cm)	150-227(193)	19 7 27 6(23 3)	6 ± 2 20	28 ± 2.74	8
Internal mediu n	35- 99(71)	4 1 12 4(8 5)	2 ± 0.243	33 ± 1.87	13
I ddles (8 cm)	100-163(130)	11.2 25 0(17 1)	6 ± 1 44	38 ± 2.42	13
	164-227(192)	16 9-27 6(22.3)	14 ± 2 93	37 ± 2.15	9
Internal	35- 75(63)	4 1 11 3(7 3)	13 ± 2 98	55 ± 2.34	9
Small (5 cm)	76-104(90)	9 8-15 0(12 1)	12 ± 3 95	85 ± 1.89	4

*Within defibrillation modes, these means are significantly different from each other at the 5 per cent level of p.

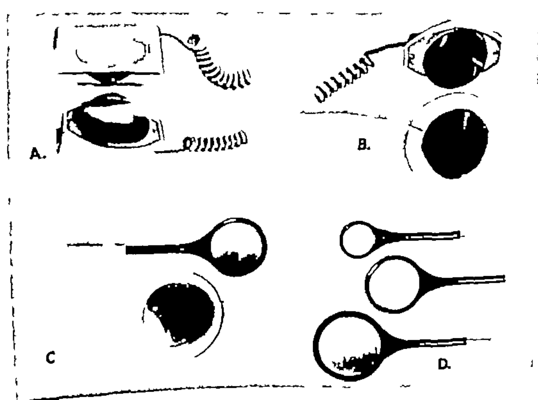


Fig 1 Photograph of various electrodes utilized this study 1 External electrodes. *B* External \ I electrodes. *C* Internal-external electrodes. *D* Internal lectrodes

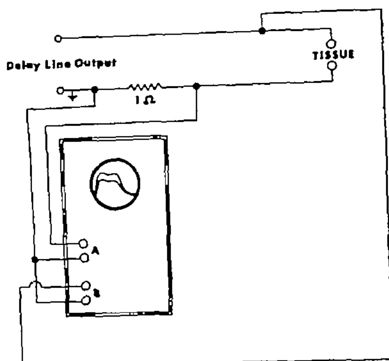


Fig 2 Diagram of instrumentation used to define delivered defibrillator interelectrode energies and resistances.

which successfully defibrillated the heart on the first shock.

Two different electrode (paddle) modes were utilized for both external and internal defibrillation. *In the external bilateral mode* (I in Table I) a pair of electrodes 9 cm. in diameter (Fig 1 *A*) were pressed against the lateral aspect of the thoracic cage over the heart the ball-joint electrode support facilitated electrode-skin contact. In the anterior posterior approach (mode II Table I) one special 9 cm electrode (Fig 1 *B*) was placed infrascapularly and the other midsternally In the latter mode contact was achieved by downward pressure on the anterior paddle. In all cases a saline pad was interposed between external paddles and the skin

In the internal-external mode III a 9 cm posterior paddle lies under the animal as in mode II and the medium-sized internal circular spoon-shaped electrode paddle contacts the heart (Fig. 1 *C*) The internal paddles are of three sizes as depicted in Fig 1 *D* The three internal modes (IV V and VI) differ only in terms of size of the internal paddles placed *around the heart* Firm pressure was applied to squeeze the heart between these paired electrodes. In some cases, an animal's size prohibited the use of the large internal paddles.

Body temperature in all dogs was maintained above 37° C with a heating pad. Venous blood pH was frequently monitored and kept above 7 31 by intravenous administration of sodium bicarbonate solution.

Equipment and calculations Tissue resistance between the defibrillator electrodes was determined essentially by the technique described by MacKay and Leeds[14] as follows. A Tektronix 502A dual-beam oscilloscope and the associated circuitry depicted in Fig 2 were employed to display the wave forms from which were computed the delivered defibrillator interelectrode energies and resistances. Inputs into the oscilloscope were single-ended in both cases. Beam A of the oscilloscope measures the potential drop across a precise 1 ohm resistor interposed in the ground lead in series with the tissue load and thus measures current (in amperes) flowing in the circuit. Beam B measures the voltage between the defibrillator paddles. These simultaneous displays were photographed

Table I Mean defibrillation thresholds and interelectrode resistance in dogs

Defibrillation mode	Heart weight range (mean) (Gm.)	Body weight range (mean) (Kg)	Mean delivered effective" threshold energy ± S.E.M (W S)	Mean interelectrode resistance ± S.E.M (ohms)	No of dogs
External	35- 99(68)	4 1 14 7(8 6)	30 ± 3 25	70 ± 3.25	39
Bilateral	100-163(128)	11 1 25 0(15 7)	40 ± 4 77	77 ± 5 41	18
	164-277(173)	11.3-27 6(21 8)	49 ± 8.14	74 ± 7 09	12
External	35- 99(73)	5 6- 9 8(7 8)	32 ± 10.54	95 ± 10.53	3
Anterior posterior	100-163(132)	11.2 19 0(14 6)	50 ± 12 41	105 ± 5 74	5
	164-227(197)	19 7 25 0(22 7)	75 ± 13 10*	97 ± 10.19	5
Internal	100-150(123)	11.2 19 0(15 8)	7 ± 2.34	98 ± 4.36	3
External	150-227(197)	19 7 24.3(22.1)	10 ± 2 66	66 ± 11.25	5
Internal	100-150(131)	11 2 25 0(17 4)	2 ± 2 24	29 ± 3 06	10
Large paddles (10 cm)	150-227(193)	19 7 27 6(23 3)	6 ± 2 20	28 ± 2.74	8
Internal medium	35- 99(71)	4 1 12.4(8.5)	2 ± 0 243	33 ± 1.87	13
Paddles (8 cm)	100-163(130)	11.2 25 0(17 1)	6 ± 1 44	38 ± 2 42	13
	164-227(192)	16.9-27 6(22.3)	14 ± 2 93	37 ± 2 15	9
Internal	35- 75(63)	4 1 11.3(7.3)	13 ± 2 98	55 ± 2.34	9
Small (5 cm.)	76-104(90)	9 8-15 0(12.1)	12 ± 3 95	85 ± 1 89	4

*Within defibrillation modes, these means are significantly different from each other at the 5 per cent level of p.

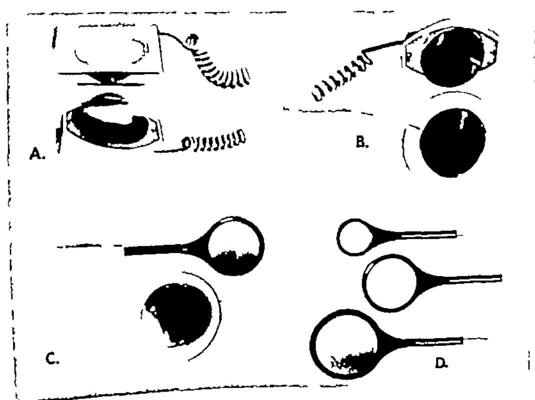


Fig 1 Photograph of various electrodes utilized in this study A External electrodes. B External A P electrodes. C Internal-external electrodes. D Internal electrodes.

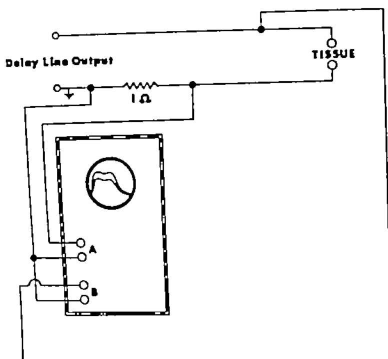


Fig 2 Diagram of instrumentation used to define delivered defibrillator interelectrode energies and resistances.

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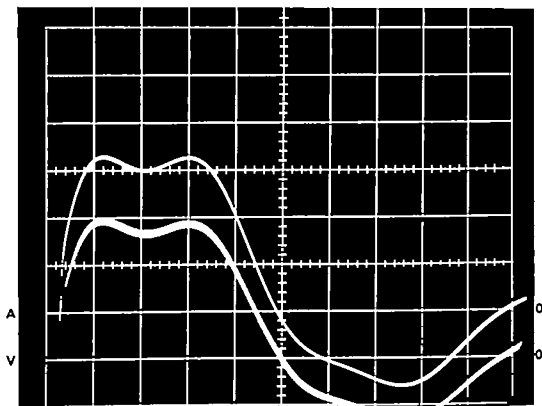


Fig 3 Simultaneously photographed displays of current (upper) and voltage (lower) i a typical wave-form discharge. Each square = 1 cm. In this example of an internal discharge, ordinate = 50 volts per centimeter or 2 amperes per centimeter abscissa is 2 msec. per centimeter

with a Polaroid oscilloscope camera as in Fig 3 Interelectrode tissue resistance was calculated as Beam B wave-form peak voltage divided by Beam A wave form peak current without regard for the small error associated with the negligible voltage drop through the one ohm resistor in series with the tissue resistance.

The total effective energy in W S delivered between the electrode paddles, E_D was estimated from the equation E_D = Peak voltage peak current t The latter term was derived as follows to obviate repetition of the laborious task of integrating these complex voltage and current wave forms, which possess constant durations and general contour for each measurement an equivalent power square wave was substituted in calculation of delivered energy This substitute equivalent square wave form was one having the same amplitude as the peak of the delay line power pulse and of such duration as to result in its containing the same amount of energy (graphically integrated voltage current curve) contained in the complex discharge power wave form This duration was found to be 0 0072 second and was constant over the complete 20 to 125 ohm resistance range through which data were taken

When the wave form overshoot (reverse current and voltage) were eliminated by a clipper circuit there was no statistically significant change in external or internal defibrillatory efficiency Only a small fraction of the total delivered energy resides in the overshoot portions of the discharge.

Results

A Interelectrode resistance The results summarized in Table I indicate that transthoracic or transcardiac interelectrode resistance is determined primarily by (1) defibrillation mode external vs internal (2) external electrode contours and sizes, as these may determine the degrees or adequacy of skin contact (defibrillation modes I vs. II e.g) and (3) the internal electrode size as this factor may influence current density through the heart. However heart size over a range of 35 to 227 Gm is not a determinant of transcardiac resistance so long as the defibrillation electrodes are

Table II Significance levels (heart weight constant)

Mean heart wt. (Gm.)	Paddle size	Resistance	Large paddle vs. medium paddle	Medium paddle vs. small paddle	Mean heart wt. (Gm.)	Paddle size	Internal threshold (W-S)	Large paddle vs. medium paddle	Medium paddle vs. small paddle
71	Small	70		$p < 0.001$	71	Small	12.5		$p < 0.01$
71	Medium	33			71	Medium	2		
130	Medium	34	$p < 0.05$		130	Medium	6	N.S.	
131	Large	29			131	Large	3		
192	Medium	37	$p < 0.05$		192	Medium	14	$p < 0.05$	
192	Large	25			193	Large	6		

held constant in terms of size and are not underdized similarly the size of the dog does not determine transthoracic resistance (Table I)

Transthoracic interelectrode resistance was about 75 ohms when the 9 cm. external electrodes were held forcefully in contact with the lateral aspects of the thoraces of dogs during defibrillation. The use of the anterior posterior electrodes was associated with an increased resistance with mean values of about 100 ohms this increase is presumably related to poor contact of the posterior paddle w th the skin in the infra scapular area, the increased distance be tween electrodes, and increased diffusion of current through additional tissue mass.

Transcardiac resistance for the internal modes ranged from 28 to 85 ohms depend ing on paddle size. The significance levels in Table II reveal that differences in mean transcardiac resistances of hearts of similar weights are related to the size of the elec trodes chosen for internal defibrillation. When large internal paddles are used transcardiac resistance is some 9 ohms less than in the same hearts defibrillated with medium-sized paddles. In turn the use of the smallest internal paddles is accompanied by an approximate 40 ohms rise in resistance. The higher resistance with defibrillation modes II or III may be attributed to poor skin contact of the posterior paddle.

B Delivered effective threshold energy The principal factors that influence the magnitude of delivered "effective" thresh old defibrillation energy include (1) defibrillation route (mode) (2) electrode area selected for the internal modes and (3) cardiac size or body weight. Because interelectrode resistance is quite constant over a broad range of body weights and heart sizes (Table I) such interelectrode resistance has no bearing on the observed differences in threshold energies provided that electrode size and character are held constant.

Mean effective threshold energies by the most convenient external route (mode I) were in the range of 30 to 50 W S delivered between the external electrodes. Fig 4 depicts the highly significant positive cor relation between heart weight and body weight of dogs used in our experiments as well as the equation of the least square regression line relating these parameters. Similarly a significant correlation ($p < 0.001$) was found to exist between external defibrillation energy threshold and body weight (Fig 5) The least squares regression line relating these parameters has the equation $Y = 2.92X - 2.29$ where $Y =$ external threshold energy in watt-seconds and X is the body weight in kilograms. It is important to point out that Y as defined by this equation represents only the aver age threshold energy that will defibrillate about 50 per cent of dogs of a given body weight. Approximately 35 W S must be added to the calculated value of Y to arrive at an energy level which will defibrillate 95 per cent of the dogs of a given body weight.

The defibrillation mode II threshold energies were extremely variable because of

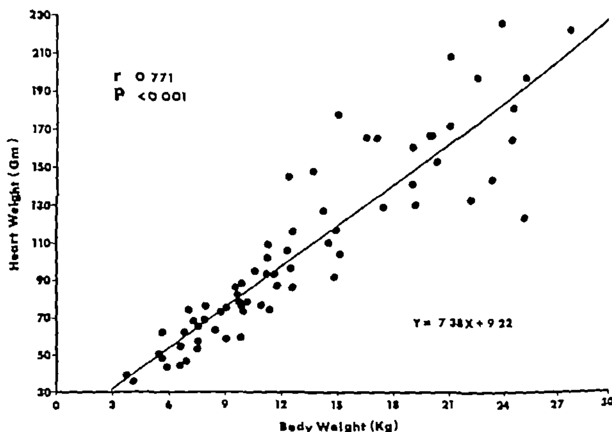


Fig. 4 Scatter plot relating heart size to body weight in dogs utilized in this study

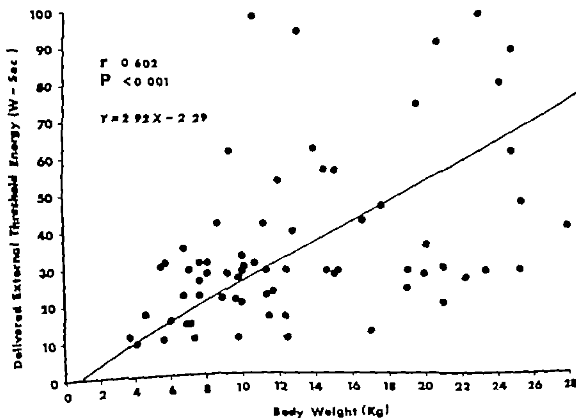


Fig. 5 Scatter plot relating delivered threshold energy to body weight in dogs defibrillated externally

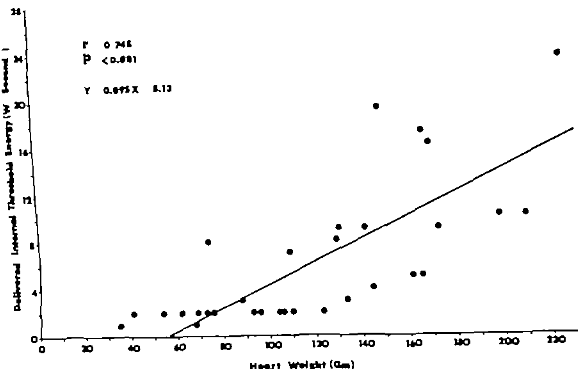


Fig. 6. Scatter plot relating delivered threshold energy to heart weight in dogs defibrillated internally with medium-sized (8 cm.) electrodes.

difficulty in achieving good skin contact with the posterior paddle in the dog. Nevertheless, there is strong evidence once again that increasing tissue mass (heart size or body weight) is correlated with an increased defibrillation energy requirement (Table I).

With medium-sized paddles (8 cm.) chosen for *internal defibrillation* delivered threshold energies may range as low as 1 W S which was adequate to defibrillate two dogs with hearts weighing 35 and 65 Gm. The highest energy required was 28 W S in a large dog with a heart weighing 227 Gm., the largest heart encountered in this series. When the largest (10 cm.) internal electrodes were utilized for internal defibrillation of the same large dog, a threshold energy of only 5 W S was adequate to defibrillate on the first shock. Inspection of data in Table I permits the conclusion that a reciprocal relationship exists between the size of internal paddles and the delivered threshold energy requisite for reversion of fibrillation in hearts of a given size. Delivered defibrillation threshold energy was significantly correlated ($p < 0.001$) with heart size (Fig. 6) when the medium-sized paddles were utilized. These parameters were interrelated with a least squares regression line whose equation is $Y = 0.095X - 5.13$ where Y = threshold energy in watt-seconds and X = heart weight in grams. About 10 W S of delivered energy must be added to this calculated Y to approximate an energy level which will internally defibrillate 95 per cent of dogs with a given heart weight.

Discussion

The transthoracic body resistance of about 75 ohms determined in our experiments agrees well with that determined by MacKay and Leeds.[19] That little or no effective reactance is encountered, such as that which might be expected if the opposite chest walls were behaving like capacitor plates, has been documented by close inspection of simultaneously photographed current and voltage wave forms as previously described. Such inspection revealed no perceptible phase shift between these two wave forms.

Further, it has been determined in a

Table III Mean values of delivered threshold voltage current and energy pulse duration and stored energy (20 to 25 Kg dogs)

Parameter	*Peleska s data, condenser discharge through a coreless conductor (L = 0.29 henry R = 27 ohms)*			*Monopulse 107 (L = 0 4 henry R = 34 ohms)*
Capacitance (µF)	24	32	35	35
Capacitor voltage (volts)	2,300	1 800	1 700	1 950
Voltage delivered at electrode	510	530	540	715
Delivered current (amperes)	16 0	13 7	13 9	9.8
Load resistance (ohms)	32	39	39	73
Pulse duration (msec.) at baseline	10.0	11 7	16.3	12.0
Delivered energy (W S) *Energy* = $(E^2/R)t$	38	34	55	50
Capacitor stored energy (W-S) *Energy* = $\frac{1}{2} CV^2$	64	51	72	67

large series of dogs that up to 60 seconds of fibrillation does not alter transthoracic interelectrode resistance as compared to that in dogs fibrillating for only 15 seconds Neither is there any difference in resistance encountered between dogs with fibrillating versus nonfibrillating hearts (unpublished data)

With internal paddles of adequate size the measured resistance of hearts weighing up to 227 grams was of the order of 30 to 35 ohms. The relationship of electrode size defibrillation effectiveness and electrical resistance of tissues has been aptly discussed many years ago by Guyton and Satterfield [11] who state The pathway of current flow through solid media is not a straight line between the two electrodes, but much of the current swings in wide arcs as do the lines of force between the two poles of a magnet. However in contrast to the effect with small electrodes it can be shown that very large electrodes will cause collimation of current flow between the mid portion of the electrodes and the arching of current will occur mainly from the edges Therefore electrodes larger than the heart itself theoretically will cause the greatest density of current through the heart for a given voltage. This explains our findings of a reciprocal relationship between internal electrode size and tissue resistance as well as delivered effective threshold energy

Delivered external defibrillation threshold energies in dogs ranged from a minimum of 9 W-S in a dog weighing 4 1 kilograms to 100 W-S in a large-chested dog weighing 22 5 kilograms. The mean delivered threshold energy values quoted in Table I for the small intermediate and large hearts agree well with those that may be ascertained from the work of Peleska.[4] It was possible to estimate that 38 to 55 W-S of delivered energy were required to defibrillate Peleska s large dogs, which received discharges from a single section capacitor inductor circuit containing the three most advantageous capacitances as judged by him This was done by graphical and numerical integration of the products of the reported voltage and current parameters over the time period of his discharge wave form The wave form from the defibrillator used in the present studies compares favorably in terms of the several parameters measured by Peleska for his optimal coreless inductor altered discharges (Table III) Peleska s lower tissue resistance values may be explained by his use of external electrodes having about 4 times the surface area of the electrodes utilized in the present study

The mean delivered threshold energies required for defibrillation of the larger hearts in our series were surprisingly low when the largest (10 cm) internal electrodes were utilized In most cases less than 10 W-S were required However it became very difficult and often impossible to defibrillate these larger hearts with the small paddles. Thus there are no data reported for large hearts in defibrillation mode VI in Table I and the importance

of selection of the largest electrodes compatible with their insertion into a thoracotomy or pericardial cradle is emphasized.

Use of the external anterior posterior mode on dogs presents certain obvious disadvantages related to the anatomical configuration of the thorax and back of this species. The poorer contact and higher resistances encountered in this species may not carry over to the clinical patient with a flatter wider infrascapular area. This approach has been advocated in clinical situations by some investigators who have the impression of lower threshold energies required.

The relatively low thresholds found with the internal-external approach support its clinical use, especially in those patients with posterior adhesions precluding internal placement of a posterior paddle without extensive dissection.

Summary

A new DC defibrillator with a unique discharge wave form emanating from a two-stage delay line was used to delineate internal and external delivered threshold defibrillation energies and tissue resistances in anesthetized dogs. These parameters were calculated from interelectrode potentials and currents simultaneously photographed from a dual-beam oscilloscope. It is important to determine delivered energy thresholds and not to rely on capacitor stored energy thresholds because of several potential avenues for energy losses in experimental and clinical situations. Threshold energies ranged from 10 to 100 watt seconds (W-S) externally and from 1 28 W-S internally. Defibrillation threshold is closely correlated with body size for external routes. When electrode size and character are held constant, it is correlated with heart size for internal routes. Transthoracic resistance in the dog is of the order of 75 ohms and cannot be correlated with body size or weight. Transcardiac resistance is in the neighborhood of 30 to 35 ohms. Internal interelectrode resistance is determined principally by electrode size; increased resistances and energy thresholds are encountered for hearts of a given size if the electrodes are grossly undersized.

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Electrocardiographic and hematological changes by exercise test in coronary patients and pyridinolcarbamate pretreatment. A double-blind crossover trial

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Master's two-step exercise test has been extensively used all over the world almost without any danger. However, in patients with advanced atherosclerotic lesions in their coronary vessels, unaccustomed strong exercise certainly may induce some injuries in coronary blood vessels, and it is also true that the exercise test performed carelessly in patients suffering from coronary sclerosis sometimes induces an attack of coronary thrombosis.

In accordance with this fact, the authors found that the adhesive platelet count is reduced and the one-stage prothrombin time shortened immediately after Master's two-step test, in addition, the well known electrocardiographic (ECG) and clinical changes in patients suffering from angina pectoris are present.[1] For such a thrombogenic tendency induced by Master's exercise test, the pathophysiologic mechanism involved is not known and there is no known drug capable of inhibiting such a response in man.

Recently, the authors[1,2] found a new group of antiatherosclerotic and antithrombotic substances which inhibits the acute vascular changes induced by mechanical as well as chemical stresses and inhibits the formation of platelet leukocyte thrombi but does not interfere directly with the fibrinogen fibrin system. Pyridinol carbamate is one of such types of compounds. In order to analyze the pathophysiologic mechanism involved in above-mentioned responses of coronary patients to the exercise test and also to see whether pyridinolcarbamate would have any inhibitory influence on the responses to Master's exercise test, pretreatment of patients suffering from coronary sclerosis with pyridinolcarbamate was subjected to the investigation in this double-blind crossover trial.

Materials and methods

Forty hospitalized patients with angina pectoris were included in this study. There

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were 25 men and 15 women with ages ranging from 37 to 75 years (mean and standard error was 55.2 ± 1.5 years) Ten patients experienced angina at rest while the other 30 patients experienced angina only during or after moderate exercise Nine patients had anginal attacks more than three times a day 15 patients one to two times a day and the other 16 patients at least once a week. Administration of nitroglycerin was effective in relieving anginal pain in 38 cases. Complications observed were as follows 9 cases of hypertension (essential hypertension) 8 cases of old myocardial infarction, 7 arrhythmias (auricular fibrillation in 3 auricular premature beat in 2 and ventricular premature beat in 2) and 3 cases of mild diabetes mellitus. ST T segment changes such as ST depression or inverted T wave were observed in 18 cases while at rest Twenty two patients showed no changes in their resting ECG s.

The patients performed Master s two-step test[3] twice a week and other drugs were withheld during this time. One of the doctors (H Y) was designated a conductor and decided whether the first pretreatment was to be with placebo or pyridinolcarbamate by the random table. The doctors who performed the clinical and laboratory tests were not informed of the agent given as the pretreatment. The first exercise test was performed three hours after oral administration of either 1 0 Gm of pyridinolcarbamate (Banyu Pharmaco Co. Ltd. Tokyo, Japan each tablet contains 0.25 Gm. of pyridinol carbamate) or placebo containing starch powder The initial trial used the double-blind technique. One week after the first exercise test the second test was performed after administration of the alternative substance Thus, the patient who was given placebo-pretreatment for the first test, was given pyridinolcarbamate pretreatment for the second test, the end result being a within subject comparison between placebo and pyridinolcarbamate in the form of a double blind crossover test

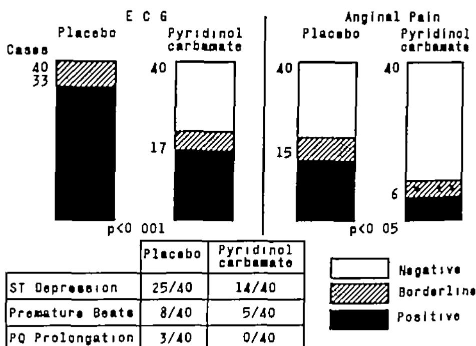
The tablets were given early in the morning on an empty stomach and the patient kept at bed rest until exercised Three hours after pretreatment the patients were exercised utilizing Master s two-step test. Electrocardiograms which consisted of Leads I II III V_1 V_4, and V_6 were taken before, immediately after and 3 5 7 10 and 30 minutes after the exercise test. The ECG was taken by three channels of electrocardiograph (Nihon Koden MC 33) Complaints and symptoms such as anginal pain and changes in blood pressure were continuously monitored.

Twenty of the 40 patients were selected at random (13 men and 7 women with ages ranging from 37 to 74 years, average 54 1 ± 1.8 years) to supply 2 ml. of blood drawn from cubital vein via a siliconized needle and syringe before and one, 10 and 30 minutes after the exercise. Using these blood samples, the following measurements were made platelet count by Olef's[4] method adhesive platelet count by Moolten and Vroman s[5] method, one stage prothrombin time using Gergy s thrombokinase[6] and calcium clotting time. One-stage prothrombin time was described as prothrombin activity for comparison between pre-exercise values of each group. At the same time, 39 healthy volunteers (24 men and 15 women ranging in age from 21 to 66 years average 39 0 ± 2 4 years) performed Master s two-step test 3 hours after oral administration of placebo and the blood coagulability and platelet count was measured as in the case of the coronary sclerotic patients.

Ischemic ECG changes, anginal attacks, and changes in blood constituents after the exercise test were compared between the first and second tests in all patients. The positive ischemic ECG changes were defined as follows appearance of ST T depression (over 0 15 mv) inversion of T wave, prolongation of P-Q interval, or appearance of arrhythmias such as premature beats. Less than 0 15 mv of ST T depression was defined as a borderline response.

Results

1 ECG findings and anginal pain. Of the 40 patients who had received placebo the exercise test induced ischemic ECG changes in 33 cases within 10 minutes of the exercise. The changes noted were definite ST T depression in 25 inversion of T wave in 3 auricular premature beat in 5 ventricular premature beat in 3, and



	Placebo	Pyridinol carbamate
ST Depression	25/40	14/40
Premature Beats	8/40	5/40
PQ Prolongation	3/40	0/40

Fig 1 Within-subject comparison between placebo and pyridinolcarbamate on prevention of ECG findings and anginal pain induced by exercise test. *Left* Number of patients who showed ischemic ECG changes (black area) induced by Master s two-step test after pretreatment with placebo or pyridinolcarbamate (within-subject, double-blind comparison) The difference noted between placebo and pyridinolcarbamate was statistically significant at p < 0 001 *Right* Number of patients who complained of anginal attacks under the above-mentioned conditions. Aga n the difference was tatistically significant between placebo and pyridinolcarbamate (p < 0 05)

prolongation of P-Q interval in 3 Borderline response was observed in 7 cases On the other hand the same test performed *after pretreatment* with pyridinolcarbamate on the same subjects resulted in only 17 cases of ischemic ECG changes namely ST T depression in 14 inversion of T wave in 2 auricular premature beat in 3 and ventricular premature beat in 2 Borderline response was observed in 4 cases. The difference between the two groups was statistically significant at p < 0 001 (Figs. 1 and 2) Anginal pain was observed in 15 of 40 patients pretreated with placebo within 10 minutes of the exercise test, while only 6 of the same 40 patients pretreated with pyridinolcarbamate complained of anginal pain This observation was also statistically significant at p < 0 05 (Fig 1)

There was no difference between the two treatment groups when pulse rates were compared following the exercise test Three hours after the oral administration of placebo the patients pulse rates averaged 66 0 ± 7 7 per minute (average and standard error) The pulse rates of the same subjects after receiving pyridinolcarbamate averaged 64 2 ± 3 6 per minute. Immediately after the exercise test the pulse rate of the patients pretreated with placebo increased to 130.8 ± 5 0 per cent of the pre-exercise value Three minutes after exercise the pulse rate was 106.3 ± 2.2 per cent it was 103 9 ± 2 0 per cent at 5 minutes 104 7 ± 2 0 per cent at 7 minutes and 101 9 ± 2 5 per cent of the pre-exercise value 10 minutes after exercise. The pulse rates after exercise of the same subjects pretreated with pyridinolcarbamate were as follows 129 7 ± 4.8 per cent immediately after 107 6 ± 1 9 per cent 3 minutes after 104 0 ± 1 5 per cent 5 minutes after 101 7 ± 1 8 per cent 7 minutes after and 102 0 ± 2 1 per cent of the pre-exercise value 10 minutes after the Master s test. There was no significant difference in the percentages between the two treatments. The observed changes in blood pressure between the two treatments were not statistically significant

Twenty three of the 40 patients were given placebo and the other 17 patients were given pyridinolcarbamate for the

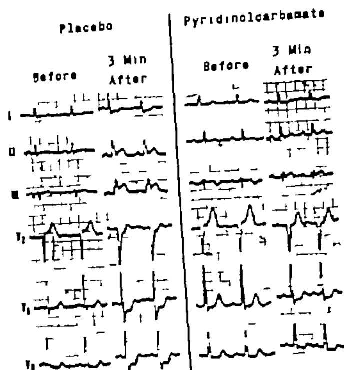


Fig. 2. Exercise ECG changes under placebo and pyridinolcarbamate treatment. *Left.* In 65-year-old man pretreated ith placebo, there were ischemic ECG changes 3 minutes after the exercise test. *Right.* These changes are prevented by pretreatment with pyridinolcarbamate.

first exercise test. During the first exercise test, 20 of the 23 patients pretreated with placebo developed positive ischemic ECG changes while 7 of the 17 patients pretreated with pyridinolcarbamate developed positive ECG changes. During the second exercise test, 13 of 17 patients pretreated with placebo showed positive ischemic ECG changes while 10 of 23 patients pretreated with pyridinolcarbamate showed the positive ECG changes. There was no significant difference between the appearance of ischemic ECG changes and the arrangement of placebo and pyridinolcarbamate.

2. Changes in blood coagulability and platelet count. In 20 patients selected at random from the above 40 subjects pretreated with placebo, the prothrombin activity was 98.4 ± 1.6 per cent, calcium clotting time was 105.8 ± 2.8 sec., platelet count was (271 ± 16) × 10³ per cubic millimeter adhesive platelet count was (137 ± 9) × 10³ and nonadhesive platelet count was (134 ± 8) × 10³ per cubic millimeter (average ± standard error) before the exercise test. The same measurements in 39 healthy volunteers were as follows prothrombin activity was 96.7 ± 2.1 per cent, calcium clotting time was 119.9 ± 5.5 sec platelet count was (301 ± 13) × 10³ per cubic millimeter adhesive platelet count was (149 ± 7) × 10³ per cubic millimeter and nonadhesive platelet count was (153 ± 8) × 10³ per cubic millimeter respectively. A statistically significant difference at $p < 0.01$ and 0.05 was observed when the calcium clotting time and platelet count was compared between healthy volunteers and patients with angina pectoris. After pretreatment with pyridinolcarbamate the same 20 subjects had the following test results before exercise 99.1 ± 1.8 per cent in prothrombin activity 106.5 ± 2.3 sec. in calcium clotting time (277 ± 17) × 10³ per cubic millimeter in platelet count, (134 ± 9) × 10³ in adhesive platelet count, and (143 ± 10) × 10³ in nonadhesive platelet count. There were no significant changes

Table I Changes in blood coagulability and platelet count induced by Master's two-step test

Treatment	Parameters	Before exercise (Mean ± S.E.)	Per cent change after exercise (Mean ± S.E.) 1 min.	10 min.	30 min.
		Healthy (39 cases)			
	One-stage prothrombin time	96 7 ± 2 1%	95 8 ± 0 5	100 5 ± 0 4	100 3 ± 0 2
	Calcium clotting time	119 9 ± 5 5 sec.	90 2 ± 0 7	100 4 ± 0 2	100 0 ± 0 1
Placebo	Total platelet count	(301 ± 13) $\times 10^3$	98 8 ± 0 9	99 4 ± 0 7	100 7 ± 0 5
	Adhesive platelet count	(149 ± 7) $\times 10^3$	97 9 ± 3 6	98 2 ± 3 4	104 1 ± 2 4
	Nonadhesive platelet count	(153 ± 8) $\times 10^3$	99 1 ± 3 8	99 3 ± 0 8	99 5 ± 1 6
		Angina pectoris (20 cases)			
	One-stage prothrombin time	98 4 ± 1 6%	93 7 ± 0 4	99 9 ± 0 4	99 8 ± 0 1
	Calcium clotting time	105 8 ± 2 8 sec.	88 5 ± 0 8	100 6 ± 0 7	99 6 ± 0 5
Placebo	Total platelet count	(271 ± 16) $\times 10^3$	86 5 ± 2 3	91 9 ± 1 3	98 6 ± 1 4
	Adhesive platelet count	(137 ± 9) $\times 10^3$	74 6 ± 4 5	83 7 ± 2 6	94 7 ± 2 5
	Nonadhesive platelet count	(134 ± 8) $\times 10^3$	99 5 ± 1 6	94 4 ± 5 2	101 3 ± 1 4
	One-stage prothrombin time	99 1 ± 1 8%	99 7 ± 0 2	99 7 ± 0 2	100 1 ± 0 2
Pyridinol carbamate	Calcium clotting time	106 5 ± 2 3 sec.	99 0 ± 0 3	99 6 ± 0 4	99 5 ± 0 4
	Total platelet count	(277 ± 17) $\times 10^3$	93 8 ± 1 3	96 3 ± 0 9	98 4 ± 0 6
	Adhesive platelet count	(134 ± 9) $\times 10^3$	88 2 ± 2 3	94 1 ± 2 1†	97 8 ± 1 5
	Nonadhesive platelet count	(143 ± 10) $\times 10^3$	99 3 ± 1 0	93 5 ± 5 0	100 2 ± 1 0

One-stage prothrombin time of pre-exercise value as described as prothrombin activity
P < 0.01
†P < 0.05 (compared to pre exercise value)

in blood coagulability and platelet count between the two pretreatments.

One to 10 minutes after the exercise test a shortening of the one-stage prothrombin time and calcium clotting time and a decrease in the adhesive platelet count was observed in the patients pretreated with placebo (Table I) The determinations made one minute after exercise were 93 7 ± 0 4 per cent of pre-exercise value for prothrombin time 88 5 ± 0 8 per cent for calcium clotting time 86 5 ± 2 3 per cent of the total platelet count and 74 6 ± 4 5 per cent of the adhesive platelet count These changes were statistically significant when compared to the pre-exercise value (p < 0 01) Ten minutes after exercise the decrease in adhesive and total platelet count were still observable and statistically significant at p < 0 01 Thirty minutes after exercise these changes were not observed In the same 20 patients pretreated with pyridinolcarbamate the above changes were slight or not observed at all One minute after exercise the determination showed 99 7 ± 0 2 per cent of pre-exercise value for prothrombin time and 99 0 ± 0 3 per cent of calcium clotting time No significant difference was noted The adhesive platelet count decreased to 88 ? ± 2 3 per cent of the pre-exercise value one minute after exercise (p < 0 01) however its rate of decline was significantly less than found in the cases pretreated with placebo (p < 0 05) Ten minutes after exercise the decrease in adhesive platelet count was very slight compared to that observed in the cases pretreated with placebo (p < 0 05) Other changes in platelet count and blood coagulability were not observed

The shortening of the one-stage prothrombin time and calcium clotting time was observed also in the healthy volunteers one minute after the exercise while the platelet count did not change (Table I) The determinations made one minute after exercise were 95 8 ± 0 5 per cent of pre-

exercise value for prothrombin time and 90.2 ± 0.7 per cent for calcium clotting time. These changes were statistically significant when compared to the pre-exercise value ($p < 0.01$) however its rate of shortening was significantly less than that found in patients with angina pectoris pretreated with placebo ($p < 0.01$ and 0.05) Other changes were not observed in the blood coagulability and the platelet count during the experimental time of up to 30 minutes.

Discussion

The double-blind crossover trials performed in this study seemed satisfactory to exclude the influence from various individual conditions including differences in constitution living conditions, and so on, and to exclude the contamination from the prejudice of patients and examiners in this clinical study The most important finding is the statistically significant inhibitory effect of pyridinolcarbamate on the ECG changes, anginal pains, arrhythmias, and hematological changes induced by Master's two-step test.

The antiatherosclerotic effect of pyridinolcarbamate has been well demonstrated in man and animal and the ischemic ECG changes themselves and those occurring immediately after Master's two-step test have been shown to be improved in the course of long term treatment of coronary patients with the compound.[8] However it is seemingly curious that one shot pretreatment of patients with the compound exhibited the preventive effects. This compound has not been known to dilate the coronary arteries. It has neither a β-adrenergic blocking effect nor a hypotensive effect reducing the heart wall tension as further demonstrated in this experiment by its failure to produce any specific effect on the changes in pulse rate and blood pressure noted before and after exercise However this compound has been known experimentally to prevent the acute edematous changes of the arterial wall induced by chemical or traumatic stresses,[2] and at the same time some increase in the glycolytic enzymes of cardiac muscles and arterial smooth muscles has been experimentally proven.[10] Burch and DePasquale[11] suggested that ischemic myocardial tissue may liberate bradykinin which then produces the pain of angina pectoris, and pyridinolcarbamate actually shows a slight inhibitory effect toward a bradykinin induced pseudoaffective response[12] in rabbits.

In patients with severely damaged arterioles and arteries due to coronary sclerosis, traumatic injury of the local microcirculatory system may easily be induced by an accelerated heart beat following Master's two-step test and it may contribute to the ischemic changes in the ECG as well as cardiac clinical signs and also in the hematologic findings. Also the exercise may promote the liberation of epinephrine. The acute vascular injury was induced by various physical or chemical stresses such as traumatization, injection of epinephrine bradykinin or a high molecular weight substance, and oral administration of cholesterol, saturated fatty acids, or animal fat in animals, and it accompanies a transient appearance of stickiness of the vascular endothelial surface to platelets and leukocytes, microthrombi a reduction in adhesive platelet count, and a shortening in several clotting times.[13] At the same time the arterial wall shows an edematous state characterized by positive acid mucopolysaccharide staining[10] Pyridinolcarbamate has been shown to lessen or prevent such an acute vascular injury including the edematous swelling of arterial wall induced by mechanical or chemical stresses in animals.[14] In man the immediate response of volunteers either to the intravenous administration of 0.1 μg per kilogram of epinephrine or to the oral administration of 50 Gm of butter (mixed in 100 ml. of fresh cream) was a transient reduction in adhesive platelet count and a transient shortening in one-stage prothrombin time and calcium-clotting time[14] as in the case of animals. The pretreatment of the test subjects with 0.5 to 1 Gm of pyridinolcarbamate lessened or prevented statistically significantly this immediate response.[14] Spector and Willoughby[15] also reconfirmed the inhibitory activity of this compound on the acute vascular changes following experimental injury in their animals. In addition, Lykke, Willoughby and Korache[16] reconfirmed that pyridinolcarbamate inhibits the vascular-permeability-

increasing effect of bradykinin and they also found that the compound inhibits the vascular permeability-increasing effect of RNA and their lymphnode permeability factor

The changes in blood coagulability and adhesive platelet-count induced by Master's test have not been analyzed in patients suffering from coronary sclerosis until the study reported in this paper Finkel and Cumming[17] reported that exercise caused enhancement of blood coagulability and an increase in both platelet count and platelet adhesive count in healthy subjects ranging in age from 18 to 35 years. In our results on the healthy volunteers Master's two-step test caused the enhancement of blood coagulability just after exercise and no changes in platelet and adhesive platelet count On the contrary in our patients suffering from coronary sclerosis the exercise test caused not only the enhancement of blood coagulability which showed stronger response than that of healthy persons but also the decrease of platelet and adhesive platelet count although short lived The exercise of Finkel and Cumming was carried out on healthy young subjects and the grade of exercise was much stronger and longer than Master's test so that the opposite reaction in the platelet count between both experiments seems to originate from such differences.

In the present experiment patients with angina pectoris before exercise had a lower platelet count and also enhanced blood coagulability when compared with the same tests run on healthy volunteers prior to exercise. It was also found that the further enhancement of blood coagulability and the decrease in the adhesive platelet count appeared significantly just after the exercise test on coronary patients. In healthy persons the enhancement of blood coagulability which showed less degree than that found in coronary patients and no decrease in adhesive platelet count was observed after the exercise test The changes in blood coagulability and adhesive platelet count as noted after Master's test are known to be predisposing factors in the pathogenesis of thrombosis as was previously suggested by the authors[13,14] so that the inhibitory effect of pyridinolcarbamate on the hematological changes induced by Master's test suggest the antithrombotic property of this compound in man. Actually Fukui[18] reported the statistically significant preventive effect of pyridinolcarbamate against the relapse of apoplexy and myocardial infarction by his controlled trials in a large number of hospitalized patients over 4 000 patients during the past 3 5 years of the observation in their rehabilitation hospital Henry[15] reported that this compound changed the platelets in shape from discs to spheres, and lessened the vasoconstriction related to hemostasis. Such facts suggest that pyridinolcarbamate lessens the thrombogenicity involved in the pathophysiologic response of man to mechanical or chemical stresses once called the emergency reaction of man by Cannon[19] in the early stage of the investigation on thrombosis and hemostasis. Needless to say the mechanism by which pyridinolcarbamate exerts its preventive effect against clinical electrocardiographic and hematological changes induced by exercise is not yet understood however the results obtained may shed further light on the pathophysiologic mechanisms involved in cardiac and hematological responses of coronary atherosclerotic patients to exercise

Summary

Forty hospitalized patients with angina pectoris 25 men and 15 women 37 to 75 years of age were subjected to Master's two-step test Three hours before the test, 1 0 Gm of pyridinolcarbamate or placebo was given orally using a double-blind technique Before immediately after and 3 5 7 10 and 30 minutes after exercise electrocardiographic changes and clinical symptoms were observed In 20 of the above subjects prothrombin activity calcium clotting time and the platelet and adhesive platelet count was measured Thirty three of the 40 patients pretreated with placebo developed ischemic ECG findings immediately to 10 minutes after the exercise test. Seventeen of the same 40 subjects pretreated with pyridinolcarbamate developed ischemic ECG findings. The difference between placebo and pyridinolcarbamate was statistically significant at $p < 0.001$

For the second exercise test the 17 patients who had received pyridinolcarbamate for the first test were pretreated with placebo, and 13 showed positive ischemic ECG changes. The 23 patients who had received placebo for the first exercise test were pretreated for the second test with pyridinolcarbamate and 10 developed positive ECG changes. There was no significant difference noted between the two exercise tests in regard to the appearance of ischemic ECG changes. The appearance of anginal pain after exercise was prevented by pretreatment with pyridinolcarbamate ($p < 0.05$)

In comparison to other 39 healthy volunteers, the patients with angina pectoris showed enhanced blood coagulability and lower platelet count. In healthy persons, enhanced blood coagulability was observed one minute after the exercise test ($p < 0.01$) In coronary patients, the enhancement of blood coagulability which showed a stronger response than that of the healthy group and the decrease of platelet and adhesive platelet count was observed one to ten minutes after the exercise test ($p < 0.01$) These changes lessened or disappeared after pretreatment with pyridinolcarbamate ($p < 0.05$)

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Electrocardiographic changes following x-irradiation of the canine heart

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Clinical observations indicate that myocardial lesions may occur following external x ray irradiation or intracavitary radium therapy for the treatment of intra thoracic neoplasms.[1-7] Myocardial damage in the form of fibrinous pericarditis myocardial hemorrhages edema and focal necrosis have been reported by Liebow and associates[8] in victims of atomic explosions at Hiroshima and Nagasaki Cases of gross cardiac damage after accidents at nuclear installations have also been described [9,10]

Experimental studies have shown histologic changes in the myocardium at various dose levels. Hartman and associates[11] described pathologic changes in the hearts of dogs following high doses of x rays Leach and Sugiura[12] investigated the effect of single doses of x rays applied to the hearts of rats. They described myocardial damage at 7 500 roentgens and death of the animals with marked evidence of heart failure hemorrhages and intercellular edema at 10 000 roentgens. Phillips and co-workers[13] reported pathologic changes in the hearts of dogs after cardiac irradiation with 5 000 to 8 000 roentgens of x ray

Electrocardiographic studies after irradiation have been carried out on man[1-4] and experimentally on animals.[13-14] The results have been controversial and conflicting probably because they involved different animal species and humans with a variety of underlying diseases.

The present work aims mainly at studying the electrocardiographic changes produced after x irradiation of the heart of dogs.

Material and methods

The study was performed on dogs of either sex of adult age considered in good health by *veterinary* examination and kept on standard diet and standard living conditions.

For irradiation x rays were produced at 200 kv 15 Ma. having a *half value layer* of 1 7 c mm The radiation beam was directed through a cone having a portal *of* entry of 8 by 10 cm and a target skin distance of 30 cm

Dogs were anesthetized with intravenous sodium pentothal 25 mg per kilogram of body weight During irradiation they were placed in the supine position with extended

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limbs bound to the table and the cone surface aligned to an area on the anterior chest wall corresponding to the precordium.

Prior to irradiation an electrocardiogram which included three bipolar and three unipolar limb leads was taken. It was not feasible to take the chest leads because of the narrow chest of the dogs. The body position of the dogs and particularly the chest position was carefully controlled during recording of the electrocardiogram. Serum glutamic oxalacetic transaminase and pyruvic transaminase levels were determined and an anteroposterior chest roentgenogram was taken.

The electrocardiogram was repeated after irradiation at intervals of 1, 3, 7, 10, 14, 21, and 30 days and then monthly. Tracings were recorded with the dogs in exactly the same position as that taken before irradiation. The serum transaminase levels were determined at the same intervals. The chest roentgenograms were taken at six-week intervals and measured for transverse, vertical, and oblique diameters; also the cardiothoracic ratio was determined.

Twenty-eight dogs were included in the study. Of these, three were kept as control animals undergoing the same procedures except for the irradiation (sham irradiation). Twenty-five dogs were given single acute doses to the heart, ranging from 1,000 to 8,000 roentgens, at the rate of 60 roentgens per minute.

Results

Electrocardiographic changes. The three sham-irradiated dogs showed no electrocardiographic changes during an observation period of six months.

Three dogs exposed to 1,000 roentgens showed no electrocardiographic changes during an observation period of eight weeks.

Among the four dogs receiving 2,000 roentgens, one dog showed no change while the remaining three showed T wave inversion in Leads I, II, III and aV. These changes appeared on the average three days after irradiation, showed signs of regression starting two weeks after onset, and the electrocardiogram was normal four weeks after irradiation.

Three dogs were exposed to 3,000 roentgens. All presented T wave inversion in Leads I, II, III and aV_F and in one case also in aV_L. Average time of onset was four days after irradiation; regression started two weeks after onset, and all tracings reverted back to normal within four weeks after irradiation.

Among four dogs exposed to 4,000 roentgens, one dog showed no electrocardiographic changes during an observation period of 30 days. The remaining three showed inversion of the T wave in Leads I, II, III and aV_F starting three to seven days after irradiation. In two dogs the tracings reverted back to normal 35 and 37 days after irradiation though one of these dogs died 50 days after irradiation. The fourth dog died 26 days after irradiation before any signs of regression appeared.

Four dogs were exposed to 5,000 roentgens. Three showed marked T wave inversion in Leads I, II, III and aV_F starting three days after irradiation. Fig. 1 shows the electrocardiographic tracings of one of this group of dogs before and 30 days after exposure. The remaining dog showed only decreased amplitude of the R wave in all leads. All four dogs died 25 to 60 days after irradiation while the electrocardiographic abnormalities were still present.

Three dogs received 6,000 roentgens. Two showed marked T wave inversion in Leads I, II, III and aV_F and the third showed decrease of the amplitude of the R wave in all leads with S-T segment depression. Changes started on the average seven days after irradiation and were persistent when all the animals died 20 to 50 days after irradiation.

Two dogs receiving 7,000 roentgens showed deep T wave inversion in Leads I, II, III and aV_F appearing three days after irradiation and, in addition, decrease of the R wave amplitude in one dog. Both animals died 38 and 40 days after irradiation, respectively, while changes in the electrocardiogram were still present.

Two dogs were exposed to 8,000 roentgens. Both animals showed deep T wave inversion in Leads I, II, III and aV_F which appeared three days after and this persisted until the two dogs died five and seven weeks after irradiation, respectively. Table I summarizes these results.

Electrocardiographic changes following x-irradiation of the canine heart

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Clinical observations indicate that myocardial lesions may occur following external x ray irradiation or intracavitary radium therapy for the treatment of intra thoracic neoplasms.[1-7] Myocardial damage in the form of fibrinous pericarditis myocardial hemorrhages edema and focal necrosis have been reported by Liebow and associates[8] in victims of atomic explosions at Hiroshima and Nagasaki Cases of gross cardiac damage after accidents at nuclear installations have also been described[9,10]

Experimental studies have shown histologic changes in the myocardium at various dose levels. Hartman and associates[11] described pathologic changes in the hearts of dogs following high doses of x rays Leach and Sugiura[12] investigated the effect of single doses of x rays applied to the hearts of rats They described myocardial damage at 7,500 roentgens and death of the animals with marked evidence of heart failure, hemorrhages, and intercellular edema at 10 000 roentgens. Phillips and co-workers[13] reported pathologic changes in the hearts of dogs after cardiac irradiation with 5 000 to 8 000 roentgens of x ray

Electrocardiographic studies after irradiation have been carried out on man[1-4] and experimentally on animals.[13-16] The results have been controversial and conflicting probably because they involved different animal species and humans with a variety of underlying diseases.

The present work aims mainly at studying the electrocardiographic changes produced after x irradiation of the heart of dogs.

Material and methods

The study was performed on dogs of either sex of adult age considered in good health by veterinary examination and kept on standard diet and standard living conditions

For irradiation x rays were produced at 200 kv 15 Ma having a half value layer of 1 7 c.mm The radiation beam was directed through a cone having a portal of entry of 8 by 10 cm and a target skin distance of 30 cm

Dogs were anesthetized with intravenous sodium pentothal 25 mg per kilogram of body weight During irradiation they were placed in the supine position with extended

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Table 1

Dose	*No. of dogs*	*No. of dogs showing ECG changes*	*Time of appearance (days post-irradiation)*	*Time of disappearance (days post-irradiation)*	*No. of dogs died*	*Time of death (days post-irradiation)*
Sham	3	—	—	—	—	—
1,000	3	—	—	—	—	—
2,000	4	3	3	28	—	—
3,000	3	3	4	28	—	—
4,000	4	3	3 to 7	35 to 37	1	26 to 50
5,000	4	4	3	—	4	25 to 60
6,000	3	3	7	—	3	20 to 50
7,000	2	2	3	—	2	38 to 40
8,000	2	2	3	—	2	35 to 49

of the same dog before irradiation and at variable periods thereafter. Regression of changes at lower doses and their persistence at higher doses supports the significance of these changes.

Whether these T wave changes are due to myocardial or vascular effects of irradiation remains to be solved. Myocardial tissue is intrinsically radioresistant while blood vessels are relatively radiosensitive. Histopathologic changes reported in irradiated tissue included cellular and intercellular breakdown as well as alterations in the endothelial lining of the small blood vessels. This was attributed to the high absorption of radiation energy by the extracellular connective tissue particularly collagen which is significant in relation to the walls of blood vessels.[13] On the other hand Hartman and associates showed that after irradiation muscle damage occurred earlier than arterial obliteration. Whitefield and Kunkler[2] considered that electrocardiographic changes following irradiation are the consequence of direct injury to the myocardium rather than ischemia secondary to radiation arterial damage.

The absence of Q-wave changes at the dose levels studied in this work denotes that actual infarction did not occur. Myocardial necrosis however has been produced at much higher dose ranges,[14] with a significant rise in the transaminase levels.

It can therefore be concluded that the heart possesses a lower threshold to radiation damage than has previously been considered.

Summary

The effect of deep x irradiation on the canine heart at doses of 1,000 to 8,000 roentgens has been studied with reference to the electrocardiogram, serum transaminase levels, and cardiac size. T wave changes were the most conspicuous, starting at doses of 2,000 roentgens. Doses of 5,000 roentgens and above were found to be lethal. No significant change occurred in the transaminase level or cardiac measurements. The significance of these findings is discussed.

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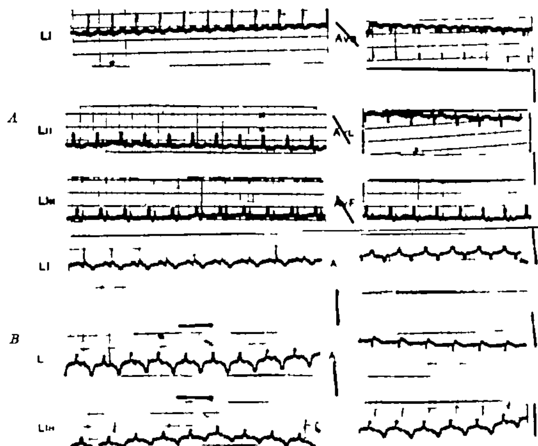


Fig 1 A Electrocardiogram of Dog 16 before irradiation. B Electrocardiogram of the same dog 30 days after cardiac exposure to 5 000 roentgens.

Serum transaminase activity The normal level of serum glutamic oxalacetic transaminase and serum pyruvic transaminase in the control dogs and in all dogs before irradiation as determined spectrophotometrically was found to be 35 ± 5 (S D) and 32 ± 6 (S D) Karmen units respectively Following irradiation of dogs at the various doses used the transaminase levels showed no significant change

Cardiac measurements Measurement of the cardiac size in the transverse longitudinal and oblique diameters as well as the cardiothoracic ratio in the control dogs and in dogs before irradiation showed no significant change after irradiation at the various dose levels employed No significant radiologic changes in the lung parenchyma were observed after irradiation

Discussion

This work shows that the threshold dose for the production of electrocardiographic alteration in the canine heart is 2 000 roentgens delivered as a single acute exposure to the precordial area. Time of onset of these changes was relatively constant in spite of various doses, being on the average three to seven days At dose ranges of 2 000 to 4 000 roentgens the changes were reversible disappearing within three to five weeks after irradiation For higher doses 5 000 to 8 000 roentgens changes persisted till death after a variable period It is therefore assumed that death was due to cardiovascular damage The main change occurring in the electrocardiogram was inversion of the T wave The degree of T wave inversion was related to the dose of irradiation deeper inversion occurring with the higher doses.

Some observers questioned the significance of T wave alteration in the dog's electrocardiogram since it is subject to individual variations[4,17] This objection is untenable in this work since results were based on comparative study of the tracings

Studies on the impulse conducting pathways in the atrium of the mammalian heart

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A supra vital staining technique, which has been demonstrated to stain preferentially the specialized tissue tracts of the atrium of the rabbit heart, has been used to survey the variation of the layout of the sinoatrial ring bundle (SARB) in the rabbit heart, and has also been applied to similar regions in the hearts of the monkey rat, and dog The findings in the rabbit heart agree with those reported in electrophysiologic studies and the results on the other animals suggest the likely existence of similar specialized properties in the hearts of these animals. In addition a number of tracts whose location is suggestive of a role in internodal conduction and which had been described previously in anatomical studies, were stained preferentially and the layout of these tracts in the heart of the four species examined is described. Both the bundle of Wenckebach and the bundle of Bachmann and its extension (as reported in the human heart by James) were observed only in the dog heart, whereas the bundle of Thorel previously reported in several animals, was present in all four species. The validity of the general use of these named tracts with reference to the hearts of these four species is discussed.

Previous studies

Despite numerous studies there remain many unanswered questions concerning conduction in the mammalian heart of the transmembrane action potential which initiates muscular contraction. There is dispute as to whether in the atrium there is a Purkinje-like system of sharply differentiated fibers which is chiefly responsible for the spread of conduction[1,2] or whether there is a spectrum of physiologic properties and structures among the atrial fibers,[3] or even whether there are any preferential conduction pathways at all in the atrium

Paes de Carvalho[4] in his work on the heart of the rabbit reported a bundle or fibers associated with the venous mouths of the right atrium This bundle was in the form of an open ring the ends of which were on either side of the atrioventricular (A V) node, and the ring itself enclosed the sinoatrial (S-A) node. This bundle demonstrated a characteristic action potential and Paes de Carvalho designated the structure the sinoatrial ring bundle or SARB In his dissection of the heart for microelectrode study the ring was severed roughly at the midpoint, and he termed the two branches thus formed the crista

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The hearts of the other animals were similarly excised but in their cases death occurred on excision of the heart.

The excised hearts were washed briefly in Tyrode solution at 37° C The tip of the ventricles was removed and the free wall of the right ventricle cut close to its ventral join to the interventricular septum The cut was continued to open the ventral wall of the smooth walled atrium and the ventromedial corner of the wall of the SVC. The right atrium was thus exposed in a manner similar to that described by Paes de Carvalho

The hearts were then stained with methylene blue dissolved in oxygenated Tyrode solution maintained at 37° C Solution strengths in the range of 0.002 to 0.05 per cent were used It was found that a strength of 0.025 per cent was optimum when light microscopy only was to be carried out, and 0.005 per cent when either or both electron microscopy and microelectrode recording were also to be attempted Staining was continued until the features were demonstrated which took between 5 and 40 minutes.

For light microscopy after staining the hearts were washed in pure Tyrode solution and were then fixed by immersion in a 2 11 per cent solution of ammonium iodide in excess ammonium picrate for 3 hours, and then immersed in saturated ammonium picrate and allowed to stand overnight.[26] Following a further 24 hours in a 50.50 mixture of glycerine jelly and saturated ammonium picrate they were mounted in fresh portions of this mixture on a microscope slide. Some photomicrographs were obtained which where useful, were assembled into montages.

Electrophysiologic examination was carried out on selected stained tissues. The still pulsating atria were pinned to a styrofoam block which was held under the surface of Tyrode solution and action potentials were recorded using approximately 0.5 μm internal diameter glass microelectrodes filled with 3M potassium chloride solution and mounted singly in a micromanipulator The output was fed through a high input impedance ($10^{12}\Omega$) amplifier to a storage oscilloscope.

Specimens for electron microscopy were dissected either immediately after staining, or after staining and microelectrode recording All specimens were approximately 1 cu mm and were precisely located with respect to the atrial anatomy Some were fixed in a 2 5 per cent solution of glutaraldehyde and postfixed in 1 per cent osmium tetroxide[26] others in 1 per cent osmium tetroxide in Krebs-Ringer buffer All were embedded in Araldite resin[27] Sections of thickness approximately 500A were cut on naked copper grids of 400 mesh stained with uranyl acetate and lead nitrate and examined in a Siemens Elmiskop I electron microscope

Results

1 Nodes Inspection of the stained preparations using a dissecting microscope revealed the S-A nodes of the rabbit, monkey and dog hearts to be characterized by a region of stained fibers which formed an intertwining network rather than bundles of fibers with a preferred orientation These fibers were narrow and tended to be spindle-shaped rather than cylindrical with the striated appearance characteristic of cardiac muscle absent or far from prominent. Action potentials with a rounded peak and prominent diastolic depolarization were recorded from this region of rabbit and monkey hearts. No attempt was made to record from the dog or rat hearts. In the case of the rat hearts, the fibers in the S-A nodal region did not demonstrate staining properties different from those found elsewhere in the wall of the SVC.

In all four species the A V node appeared as a region of longitudinally orientated stained fibers, aligned perpendicular to the A V ring and located between two regions of fibers lying parallel to the A V ring One of these regions passed along the ring the other just posterior to the mouth of the coronary sinus. Interconnections were found between fibers of adjacent regions. Action potentials close to the A V ring exhibited slight diastolic depolarization a curved foot to the depolarization phase, a decrease in the rate of depolarization before the peak of the action potential and a long time duration repolarization phase. Those from the upper A-V nodal region were similar but had no diastolic depolarization a smaller overshoot, and a quicker repolarization phase.

terminalis and septal branches respectively Some aspects of their ultrastructure have been described [7]

A number of tracts observed primarily in anatomical studies have been described and named Wenckebach[8] observed an internodal tract (the bundle of Wenckebach) in the human heart which left the S-A node from its posterior side passed across the wall of the superior vena cava (SVC) and into the interatrial (I A) septum and then travelled down the septum to end in the region of the A V node James[2] also observed this tract in the human heart Thorel[9] described a tract (now termed the bundle of Thorel) which left the posterior border of the S-A node and travelled close to the crista terminalis to the level of the coronary sinus where it divided one branch travelling on either side of the coronary sinus with the two branches ending in the A V nodal area Robb and Petri[1] observed a similar tract in the hearts of the monkey dog guinea pig and human fetus. James described it in the human heart though he mentioned only the branch which passed over the superior border of the coronary sinus He stated also that fibers from this tract passed over the pectinate muscle and that some of the fibers of the tract lay in valvular tissue around the mouth of the inferior vena cava (IVC) adjacent to the mouth of the coronary sinus Bachmann[11] described a tract in the dog heart (the bundle of Bachmann) which left the S-A node to pass over the *anterior* wall of the SVC and thence into the left atrium James described this tract in the human heart and in addition observed a branch from it which passed down the I A septum to the A V node Robb and Petri also observed a similar branch in the monkey dog guinea pig and human fetus hearts

Large polar myocardial cells have been observed in many parts of the right atrium and Robb and Petri and James stated that they formed part of the internodal paths which they described though James emphasized that no single fiber was formed entirely of such cells. There seems to be disagreement as to whether these large cells should be regarded as constituting a Purkinje like system or rather regarded as local variations of normal atrial tissue. Todd [3] Prakash [12] Robb and Petri [1] and James[2] subscribe to the former view while Cloniset[4] and Truex[5] subscribe to the latter

A number of ultrastructural studies on the S-A and A V nodes have been reported [7,13,21] and also studies on the Purkinje system [14,15,17,19,20,22] but to date little has been reported on the atrial tracts described above.[7] Mammalian S-A nodal cells are characterized by their lack of fibrillar organization abundance of unorganized filamentous material, and general appearance of arrested development. A V nodal cells are similar but perhaps even less organized and appear to vary in a somewhat complex manner with location within the nodal region Purkinje fibers have generally less fibrillar material in them than general myocardial cells, but have oriented and well-developed fibrils with a sarcoplasmic reticulum Nexus, or a tight junction between adjacent cells, a structure believed to give electrotonic continuity between the cells,[23] is sparse or absent in the nodes but present in the His bundle and the Purkinje system

It was the aim in the present study to examine these atrial tracts in the hearts from a number of mammals using a staining technique which allowed also the direct comparison of light microscopical electron microscopical and electrophysiologic characteristics.[24] Such a study was envisaged as providing further information on the previously described tracts and also some information on their ultrastructure This present paper describes the results from the staining technique as applied to four species of mammals along with some preliminary results obtained by electron microscopy Systematic microelectrode studies remain to be completed

Materials and methods

The hearts of 70 mature rabbits 7 mature squirrel monkeys 6 mature rats, 1 mature dog and 2 puppies were studied The rabbits and dogs were anesthetized by intraperitoneal injection of sodium pentobarbital the rats by application of chloroform to the snout The monkeys were anesthetized by injection of secobarbital and were then killed by an overdose of succinylcholine after which the heart was excised following opening of the chest wall

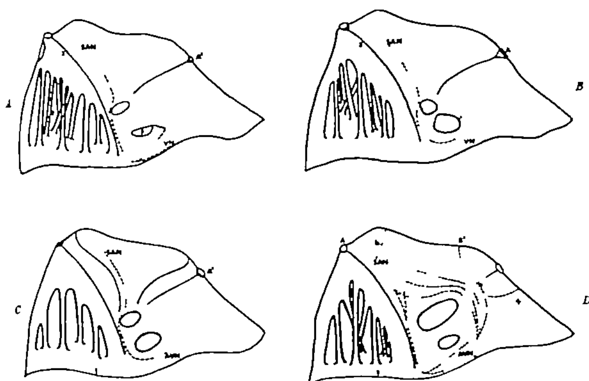


Fig. 2. As Fig. 1 except that the dotted lines indicate the stained tracts tra elling bet een the sinoatrial and atrioventricular nodes. I D B and B' are points that were adjacent before dissection, and *b* indicates the fourth tract described in the text.

fused with fibers on the crista term nalis and w th those fibers on the border of the IVC which formed part of the SARB The tract extended along the crista termi nalis until t reached the region of the A V ring Here the fibers turned medially some of them becoming continuous with fibers on the A V ring in the A V nodal region, but thers becoming continuous with fibers which passed over the upper A V nodal region just inferior to the mouth of the coronary sinus. In addition there was a diffuse path of fibers extending from the crista terminalis to pass over the pectinate muscles and onto the A V ring where they turned parallel to the ring extending into the A V nodal region where they fused w th the fibers of the first described path

MONKEY HEART

a. Tracts around the venous mouths (Fig 1 *B*) Near the crista terminalis, there was a tract of stained fibers which ppeared to be along the join of the wall of the SVC to the trium and a similar tract was observed along the join of the SVC to the interatrial septum. All of these stained fibers were set in the endocardial wall and there appeared to be no ridge or discrete bundle of tissue. Both of these tracts were continuous with stained fibers set in valvular tissue around the mouths of the IVC and coronary sinus. These latter fibers formed complete rings around each of these mouths and also an outer ring in which both the mouth of the IVC and the mouth of the coronary sinus were contained Some endocardial fibers around this ring on its atrial border were stained also The endocardial fibers, which lay along the septal border of the venous mouth turned away from the coronary sinus to end in the interatrial septum approximately 1.5 mm. from the inferomedial corner of the venous mouth In that region they interconnected with purely septal fibers and were continuous with fibers which passed over the A V node to end near the A V ring The endocardial fibers which lay along the lateral border of the venous mouths, extended beneath the mouth of the coronary sinus. Most

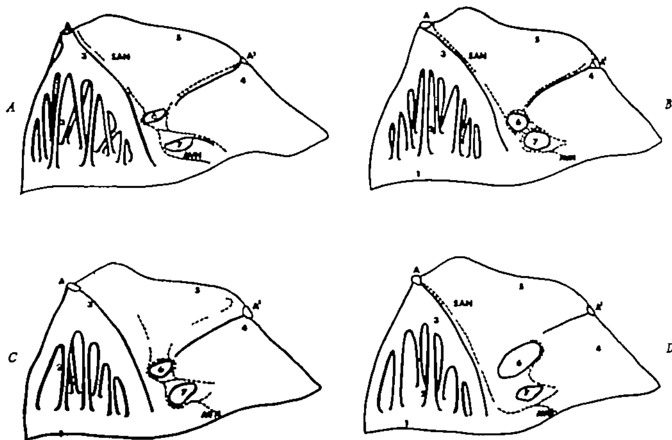


Fig 1 Drawings of the opened right atria of the hearts of (*A*) rabbit, (*B*) monkey (*C*) rat, and (*D*) dog The dotted lines indicate the stained tracts around the venous mouths. *1* = Atrioventricular ring *2* = pectinate muscle *3* = crista terminalis *4* = interatrial septum *5* = superior vena cava *6* = Inferior vena cava *7* = coronary sinus *SAN* = sinoatrial node *AVN* = atrioventricular node *A A* Indicates points on the wall of the superior vena cava which were adjacent in the intact heart before the vessel was opened.

2 *Atrial tracts* It is convenient to divide these observations into two groups (a) the tracts which pursued a course around all or part of the mouths of the veins and (b) tracts whose pathway lay between the S-A and A V nodes.

RABBIT HEART

a Tracts around the venous mouths Stained fiber tracts were located corresponding generally with the description of the SARB as given by Paes de Carvalho (Fig 1 *A*) but demonstrated some variation from specimen to specimen In approximately half the atria studied the crista terminalis branch turned medially immediately below the coronary sinus and ended along the line parallel to and approximately 1.5 mm from the A V ring usually ending as a discrete bundle but in a minority fanning out as three or more fascicles. In other atria the branch travelled inferomedially across the A V nodal region and ended near the A V ring In still others it extended caudally parallel to the crista terminalis until it reached the A V ring before it turned along the ring and ended below the coronary sinus In one specimen the branch passed across the inferior border of the coronary sinus and turned anteriorly to connect with fibers of the septal branch which had passed over the anterior and medial borders of the coronary sinus, forming in this case a complete ring around the venous mouth In all specimens examined some fibers of the crista terminalis branch were observed to pass over the anterior border of the coronary sinus and fuse with fibers of the septal branch of the anteromedial corner of the venous mouth

b Internodal tracts (Fig 2 *A*) A tract left the S-A node with an orientation parallel to the crista terminalis and 0.5 to 1 0 mm from it. It travelled caudally to the lateral border of the IVC where it

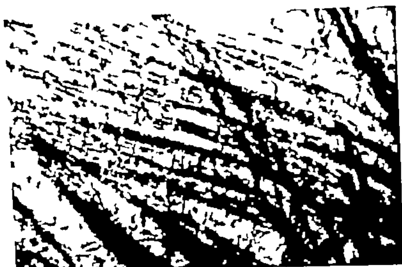


Fig. 3



Fig. 4

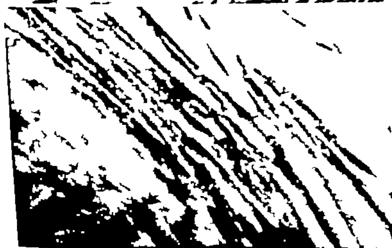


Fig. 5

Light micrograph of stained fibers in the superior vena cava of the dog heart. Here the stained fibers to 12 μm in diameter and are not rigidly straight, with most of them grouped in bundles of 5 to 20 (×150.)

Light micrograph of stained fiber in the septal wall of the rabbit heart. Here the fibers are generally ...ter and group together in larger bundles (×150.)

5 Light micrograph of stained fibers near the atrioventricular ring of the monkey heart, in the region ... the pectinate muscle. The fibers are narrower than in the regions of Figs. 3 and 4 (approximately 5 μm in ...eter). (×300.)

extended medially to interconnect with septal fibers and those extending from the medial border although some turned caudally forming connections with superficial longitudinal fibers on the atrial side of the A V node.

b Internodal tracts (Fig 2 *B*) A tract extended caudally from the S-A node parallel to and 0 5 to 1 0 mm from the crista terminalis. It passed the lateral border of the IVC where it fused with fibers on the crista terminalis and those on the IVC border described above The fibers continued caudally along the crista terminalis before turning medially 3 to 4 mm above the A V ring The fibers were continuous with fibers passing over the upper A V nodal region parallel to the A V ring and just below the coronary sinus In addition there was a diffuse pathway passing over the pectinate muscles and into the A V nodal region as in the rabbit heart.

RAT HEART

a Tracts around the venous mouths (Fig 1 *C*) A prominent system of valves around the mouth of the SVC was observed which did not appear to be drawn as far into the atrium as in the other species. The join of the wall of the SVC to the atrial wall appeared separate from the crista terminalis and from the interatrial septum Stained muscle fibers were observed in this valvular tissue and the neighboring endocardial tissue The fibers which lay around the mouth of the SVC were continuous with those which formed a complete ring around the mouth of the IVC and almost a complete ring around the mouth of the coronary sinus with the two rings fusing in the region between the two veins Some of these fibers were set in valvular tissue others were set in endocardial tissue. In a manner very similar to that observed in the case of the monkey heart, the endocardial fibers which lay along the septal borders of the venous mouths in the rat heart extended approximately 1 mm into the interatrial septum where they interconnected with septal fibers. Many of the fibers which lay along the lateral border of the venous mouths extended medially beneath the coronary sinus to interconnect with septal fibers and with those from the medial border of the venous mouths, but some formed connections with the superficial longitudinal fibers of the A V node.

b Internodal tracts (Fig 2 *C*) Approximately 0 5 mm from the border of the SVC and parallel to it (the border is separate from the crista terminalis) a tract extended from the S-A nodal region past the lateral border of the IVC to fuse with fibers of the IVC border Some of the fused fibers extended to the crista terminalis where they in turn fused with fibers of this structure extending along it to a point 1 5 to 2 0 mm above the A V ring where they turned medially to become continuous with fibers of the A V nodal region which lay parallel to the A V ring just posterior to the mouth of the coronary sinus. As in the rabbit and monkey hearts a diffuse system of fibers left the crista terminalis to pass over the pectinate muscle along the A V ring and into the A V nodal region

DOG HEART

a Tracts around the venous mouths (Fig 1 *D*) Here the join of the SVC wall to the atrium was unmarked by ridges or valvular tissue Stained fibers were present in the venous wall lying close to and parallel with the crista terminalis some of them becoming continuous with fibers on the lateral borders of the mouths of the IVC and coronary sinus some of which were set in valvular tissue. Stained fibers were seen at the join of the SVC to the I A septum but they crossed the join rather than lying along it and the join was discernible only by a slight kink in the path of the fibers. No valve tissue was present here and all the stained fibers were in the endocardium proper Most of these fibers extended medially beneath the coronary sinus and ended near the base of the interatrial septum where they interconnected with septal fibers but some turned caudally beneath the coronary sinus to connect with the superficial fibers of the A V nodal region The endocardial fibers extended from the mouth of the coronary sinus and interconnected with septal fibers.

b Internodal tracts (Fig 2 *D*) Three distinct tracts, each oriented parallel to the crista terminalis, left the S-A nodal region One was adjacent to the crista terminalis, the second 2 0 mm from it and the third 4 0 mm from it Some fibers from the first two tracts swerved medially to



Fig 3



Fig 4

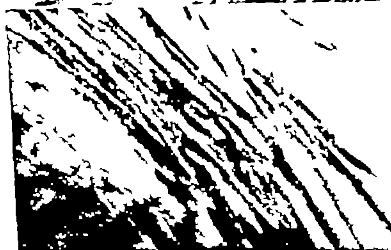


Fig 5

Fig. 3 Light micrograph of stained fibers in the superior vena cava of the dog heart. Here the stained fibers are 6 to 12 μm in diameter and are not rigidly straight, with most of them grouped in bundles of 3 to 20 fibers (×150.)

Fig. 4 Light micrograph of stained fiber in the septal wall of the rabbit heart. Here the fibers are generally straighter and group together in larger bundles. (×150.)

Fig. 5 Light micrograph of stained fibers near the atrioventricular ring of the monkey heart, in the region below the pectinate muscle. The fibers are narrower than in the regions of Figs. 3 and 4 (approximately 5 μm in diameter). (×300.)

pass by the lateral border of the SVC and fuse with fibers on the crista terminalis. The fibers extended along the crista terminalis to the A V ring where they turned medially and became continuous with fibers of the A V nodal region both along the A V ring and on the upper region of the node Fibers from all three tracts leaving the node extended from the wall of the SVC past the medial border of the IVC and into the wall of the I A septum Fibers of the three tracts fused in the lower septal wall just above the A V node They were continuous with lateral fibers passing along the upper border of the node and with longitudinal fibers which passed over the midnodal region

A fourth tract extended from the S-A nodal region in a direction approximately perpendicular to the crista terminalis extending over the wall of the SVC and into the septum further from the IVC than the other three tracts. In the diagram this tract (b) appears cut but as B and B are adjacent points separated in the preparation it forms a continuous tract in the intact heart. It extended down the septum and fused with fibers of the first three tracts just above the A V nodal region with fibers from this tract branching in the septal wall and travelling across it parallel to the A V ring As in the hearts of the other three species there was a diffuse path sweeping over the pectinate muscle along the A V ring and into the A V nodal region

3 *Structure of the fibers* Inspection of the sections by light microscopy indicated that those fibers which were set in valvular tissue did not differ noticeably in the hearts of the species examined where they were not straight, but pursued a tortuous path and occurred singly or in small bundles. The fibers were 2 to 7 μm in diameter with the diameter varying along the length and with nuclei ovoid in the larger fibers and more nearly cylindrical in the narrower ones. Fibrillar striations were not conspicuous within the fibers.

The structures of the fibers set in the endocardium also appeared consistent from one species to another and did not show significant variations with location in a given species. Many of the fibers, which were 3 to 10 μm in diameter and were straighter than those in valvular tissue occurred in small bundles or lay close to one another so that virtually all of the superficial fibers of the regions about the venous mouths were stained Intercalated discs could often be seen and they appeared to be straight rather than stepped end to-end connections being most common The nuclei were ovoid or cylindrical depending on the diameter of the cell

The structure of the fibers forming the internodal paths did not appear to vary with species, but did vary with location The fibers on the wall of the SVC were 6 to 12 μm in diameter and were not rigidly straight most being grouped in bundles of 5 to 20 fibers (Fig 3) The fibers on the septal wall were straighter and occurred in larger bundles (Fig 4) Those on the pectinate ribs and near the crista terminalis were similar but those beneath the pectinate ribs and along the A V ring were narrower (Fig 5) (approximately 5 μm in diameter) Where there was a variation in the size of the fibers there was no tendency for the larger fibers to take up the stain either more or less readily than the smaller ones.

4 *Nervous tissue.* Small nerves were observed close to some muscle fibers around the venous mouths, but they did not appear significantly more numerous in this region than elsewhere and no definite nerve endings on muscle were observed The staining of nerves and of muscle tracts was sufficiently different so that confusion was unlikely

5 *Electron microscopy* Electron microscopy has been carried out only on the discrete internodal tracts of the rabbit and rat In the rabbit there were fibers which contained few myofibrils often adjacent to smaller ones full of myofibrils (Fig 6) However such fibers were few in number and never occurred in large groups always in one or two and the majority were more nearly full of myofibrils (Figs. 7 to 9) These fibers contained at best a rudimentary T tubule system (Fig 7) and those observations could have been due to extensions of invaginations of the lateral border of the plasma membrane which were common at Z bands. There were numbers of footplates of sarcoplasmic reticulum on the lateral borders of the cells, often occurring



Fig. 6 Electron micrograph of muscle cells on the endocardial wall of the superior vena cava of the rabbit heart, showing two adjacent cells. The cell in the lower part of the micrograph is closely packed with myofibrils, whereas in the cell in the upper part of the micrograph there is a comparatively large amount of space not filled with definitive cellular components. Glutaraldehyde fixed. In this and in all the electron micrographs the bar line indicates one micron.



Fig. 7 Electron micrograph of muscle cells of the superior vena cava of the rabbit heart showing what appear to be T-tubule (*T*) although this could be on an extension of a sarcolemmal invagination (*I*) from above or below the plane of section. *F* indicates a footplate of the endoplasmic reticulum at the sarcolemma. A few atrial granules are present. Osmium tetroxide fixed.



Fig 8 Electron micrograph of muscle cells of the bundle of Thorel of the rabbit heart. Invaginations at the Z bands are marked (*I*) and footplates of sarcoplasmic reticulum at the sarcolemma are present (*F*) and the tubules of this system are seen around the fibrils. Some atrial granules (*G*) are present. Osmium tetroxide fixed.



Fig 9 Electron micrograph of muscle cells of the bundle of Thorel i the rabbit heart showing an intercellular abutment with nexus junction (*N*) and footplates of the sarcoplasmic reticul n (*F*) t the sarcolemma Osmium tetroxide fixed.

close to nexus junctions between adjoining cells (Fig 9)

In the rat there were neither cells completely devoid of or filled with myofibrils and a typical cell (Fig 10) was moderately full of myofibrils. The cells of the rat heart contained large numbers of atrial granules not observed in the rabbit heart. There was no sign of a T tubular system in the rat, though there were small numbers of invaginations of the later l w ll at Z discs. Footplates of sarcoplasmic reticulum on the lateral wall were most numerous (Figs 10 and 11) and as in the rabbit heart, often occurred near nexuses (Fig 11)

Discussion

1 The sinoatrial ring bundle The correspondence between the system termed by Paes de Carvalho the sinoatrial ring bundle



Fig. 10 Electron micrograph of muscle cells of the bundle of Thorel in the rat heart *showing an abundance of* atrial granules (*G*). Invaginations of the sarcolemma at Z bands is less marked than in the rabbit heart and there is no suggestion of a T-system. Footplates of the sarcoplasmic reticulum at the sarcolemma are present (*F*). Osmium tetroxide fixed.

and that which appears as a system around the venous mouths of the rabbit heart after staining with methylene blue has been recognized and discussed elsewhere.[24] It has been possible to describe, in the present study, systems of fibers associated with the venous mouths of monkey, rat, and dog hearts which have taken up the stain in a manner similar to that observed in the case of the SARB of the rabbit heart. Furthermore, the structure of these fibers showed a marked resemblance to that of the SARB in the rabbit heart. Detailed ultrastructural and electrophysiologic studies which would be necessary to establish whether or not these systems are completely analogous with those *in the rabbit heart have not* yet been performed but it seems convenient *to apply the term sinoatrial ring bundle to these fibers, bearing in mind that it refers* only to the correspondence in staining property and gross morphology.

The species differences in the distribution of the fibers appears to show a direct correlation with the relative prominence of the valvular tissue of the respective venous mouths. Thus the absence of a well-defined system around the SVC of the dog heart is reflected in the almost total absence of the remains of the primitive sinus venosus. The location of the system in the rat heart, *quite distant from the crista terminalis* and the join of the SVC wall to the interatrial septum reflects the fact that the sinus venosus in this species has not been completely incorporated into the atrium.



Fig 11 Electron micrograph of muscle cells of the bundle of Thorel in the rat heart showing an intercellular abutment with nexus (*N*) footplates of the sarcoplasmic reticulum (*F*) intercalated disc (*ID*) and atrial granules (*G*) Osmium tetroxide fixed.

The form and location of the system in the region of the A V node are not constant but vary from one individual to another in contrast to the clear and consistent junction between the His bundle and the node which would be consistent with the view that the specialization is different from that of the His bundle The electrophysiologic observations suggest that the SARB might provide a pathway which is more reliable (rather than significantly faster) than the surrounding tissue [6] which is consistent also with the failure to observe large fibers in the system of any of the species studied—rather the fibers were narrower than those observed elsewhere in the atrium suggesting no enhancement of conduction velocity [22]

2 *Internodal atrial tracts* Tracts of stained fibers have been observed which extended from the region of the S-A node to the region of the A V node They were continuous with fibers of the S-A node which displayed a characteristic specialized structure in the rabbit monkey and dog hearts and from which pacemaker potentials were recorded in the rabbit and monkey hearts. They were also continuous with fibers of the A V node, which were organized in a characteristic array in all four species, and from which action potentials characteristic of the slow conducting tissue of the A V node were recorded in the case of the rabbit and monkey hearts. Thus the presently available evidence favors the idea that the tracts extend from the pacemaker to the slowly conducting node at the join of the right atrium and the ventricles. The rat failed to display a specialized S-A node region which agrees with the work of Prakash [12]

Consideration of the possible correspondence between these internodal paths and those described by previous authors is complicated by the use of different techniques and species in the various studies

The bundle of Bachmann has been described in the dog heart,[11] the human heart,[4] and in the monkey dog guinea pig and human embryonic hearts[16] as has an extension from it.[3] In this present study the tract marked b in the dog heart (Fig 2 *D*) is located similarly to the bundle of Bachmann In his study of the human heart James[3] described some of the fibers of the extension as ending just above the A V node where they interconnected with fibers of other tracts, while others passed over the node to end near the A V ring This is the situation observed in the dog heart in the present study and thus it appears justified to identify this tract in the dog heart as the bundle of Bachmann and its extension

No fibers were observed to cross the join of the wall of the SVC to the septum in either the rabbit, monkey or rat hearts and thus no tract equivalent to the bundle of Bachmann was observed in these species. However there was a prominent SARB in these latter species and the superficial fibers at the join of the SVC to the septum lay along the join not across it. It appears that, at least in the species examined, where there is a prominent SARB the bundle of Bachmann is absent.

It has been suggested that the bundle of Bachmann in the human and dog hearts corresponds to the SARB in the rabbit heart.[10] Anatomically the two do not correspond. The bundle of Bachmann extends from the S-A node, while the SARB passes by it, the bundle of Bachmann extends across the join of the SVC to the septum while the SARB lies along it the bundle of Bachmann extends down the septum clear of the venous mouths, whereas the SARB hugs the venous mouths. However the bundle of Bachmann is believed responsible for the conduction of excitation to the left atrium[3,11] while Paes de Carvalho[6] observed that left atrial excitation was delayed in the rabbit heart when the crista terminalis connections to the I A septum were clamped and the fibers of the SARB were probably clamped also These observations would be consistent with functional correspondence between the two structures.

The bundle of Wenckebach has been described in only the human heart.[3] It extended from the S-A node past the anterior and medial borders of the IVC and along the I A septum to the A V node. In the present study three tracts of stained fibers were observed in a similar location in the dog heart (Fig 2 *D*) These tracts were separated in the SVC but gradually fused as they extended down the septum. It seems possible that these fibers, which have been described as three tracts when demonstrated by methylene blue staining might appear as one tract when examined by serial section. The stained fibers in the present study appeared either to end just above the A V node where they interconnected with fibers of the extension of the bundle of Bachmann, or to pass over the node and end near the A V ring These observations correspond closely to the description of the bundle of Wenckebach given by James, and it appears that these tracts described in the present study in the dog heart correspond to the bundle of Wenckebach in the human heart.

In the other species studied tracts of fibers were observed in the septum and the SVC which were located similarly to the bundle of Wenckebach. However they did not form a direct internodal link as they did not cross from the SVC to the septum but turned parallel along the join of the SVC with the septum. Thus if there were internodal conduction along their paths, it would depend on transverse conduction Also the observations of Paes de Carvalho[6] suggest that conduction does not spread from the SVC to the septum in his preparations, and support the evidence that the bundles of Wenckebach and Bachmann are not present in the rabbit atrium or at least that they do not sustain conduction.

The bundle of Thorel is an internodal path which passes by the lateral borders of the IVC and coronary sinus. It has been described in the human human embryo monkey dog, and guinea pig hearts.[3,9,10] Discussion of the possible equivalence of fibers described in this study with the bundle of Thorel will begin with the caudal reaches.

Robb and Petri described two branches of the bundle of Thorel reaching the curves of the coronary sinus and entering the A V nodal region while James[3] in human hearts observed that in some specimens some of the fibers of the bundles were set in valvular tissue around the mouth of the IVC, between it and the mouth of the coronary sinus. As these authors described the bundle of Thorel being associated with the mouth of the coronary sinus it would appear likely that the caudal reaches of the crista terminalis segment of the SARB[6] correspond with the bundle. However in each species of this present study other fibers from the crista terminalis entered the A V nodal region (Fig 2) and they were also located similarly to the bundle of Thorel. James described fibers which branched from the bundle of Thorel and spread over the pectinate muscle in the human heart. Such fibers were observed in the present study branching from the crista terminalis

Thus there seem to be grounds for suggesting that these latter fibers on the crista terminalis (Fig 2) correspond to the bundle of Thorel It may be that both the fibers of the SARB and those extending from the crista terminalis correspond to the bundle of Thorel but from this present study it appears advantageous to think of the two systems as distinct particularly as specialized properties have been assigned to the fibers on the venous mouth It seems best to refer to the fibers on the venous mouths as the SARB and those leaving the crista terminalis to spread over the atrial border of the A V node as the bundle of Thorel

At its proximal end the bundle of Thorel is described as leaving the S-A node [2,16] In this present work one SVC tract was observed which extended from the node and became continuous with fibers of the SARB and of the crista terminalis which appear to form the distal reaches of the bundle of Thorel It would therefore appear that this tract corresponds to the proximal reaches of the bundle of Thorel The fibers of the SARB and the crista terminalis by pass the S-A node and so although it appears that they form the distal reaches of the bundle of Thorel it does not appear that they form the proximal reaches Again the use of other techniques or species might suggest that the three systems should be thought of as essentially a single system but since the physiology and ultrastructure of the cells of the SARB differ from those of the other fibers, and also by anatomical observation they can be described separately it seems advantageous to retain the separate designation

In the light of the above it appears logical to use the term bundle of Thorel to define that tract of fibers which leaves the S-A node in a direction parallel to the crista terminalis which subsequently extends along the crista terminalis and then passes over the atrial border of the A V node

3 Nature of fibers forming the bundles There has long been speculation as to whether there are fibers of a Purkinje-like nature in the right atrium [18] In the present study a proportion of the fibers forming the internodal paths were wider than the majority and in the rabbit heart some of these contained few myofibrils and thus could from this point of view be said to be Purkinje-like. However these fibers were isolated individuals and did not form the whole or even a substantial part, of any internodal fiber or bundle These observations agree with those of James.[2] Thus, in general on the basis of size and degree of fibrillar development the internodal paths could not be described as Purkinje-like It may be significant that there appeared to be at best a rudimentary T system in the cells of the bundle of Thorel in the rabbit heart and none at all in the rat heart while in the rat heart there was a large number of footplates of the sarcoplasmic reticulum on the lateral walls of the sarcolemma two features which have been found in several mammals to be characteristic of Purkinje fibers as opposed to ventricular fibers.[19] Further not all of the superficial fibers of the atrium took up the methylene blue and it is possible that those which did have specialized properties. Recently it has been found in the dog heart that fibers of the bundle of Bachmann are more resistant to high K^+ concentration conduct faster and have a faster depolarization than atrial tissue [21] and like Purkinje fibers show greater than normal excitability [22]

This present work supports the view that there do exist specialized pathways in the atria of the hearts of the species examined although the nature of the specialization is still unclear It is hoped that the further application and refinement of the techniques to include electrophysiologic studies will shed further light on this problem

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Alterations in left atrial transport and mitral valve blood flow resulting from aortic regurgitation

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Information concerning the pathophysiology of aortic regurgitation has accumulated rapidly over the past five years. Measurements of pressure in the left ventricle and of blood flow in the ascending aorta have permitted a characterization of the alterations that occur in ventricular dynamics and of the various factors that influence the severity of valvular regurgitation Very little is known however of the effects of aortic regurgitation on the transport function of the left atrium During diastole the aorta and left atrium are in communication via the left ventricle and therefore it might be expected that aortic regurgitation could influence the atrial contribution to ventricular filling

A series of experiments was performed in calves before and after the production of acute aortic regurgitation Alterations in atrioventricular flow were evaluated by instantaneous measurements of mitral valve blood flow and left ventricular volume and the pressure pulses in the atrium ventricle and aorta

Methods

Calves weighing 70 to 82 kilograms were studied under halothane anesthesia. During cardiopulmonary bypass, a low profile electromagnetic flow transducer (Fig 1) with an orifice of 3 8 sq cm was sutured above the mitral valve in such a way that all blood moving between the left atrium and ventricle passed through its lumen An extravascular flow transducer (Biotronex series 3000) encircled the ascending aorta Teflon catheters 4 cm in length were placed in the ascending aorta left ventricle and left atrium These were attached to Statham P23Db pressure transducers and the transducers were driven by Sanborn 350-1100 carrier preamplifiers (Fig 2) All three transducers were balanced to zero pressure at the level of the mitral valve and calibrated in situ against a single column of mercury The static calibration was linear (± 5 per cent) from 0 to 200 mm Hg The dynamic calibration showed the following (1) The frequency amplitude response was linear (± 8 per cent) to 25 c p.s. (2) the

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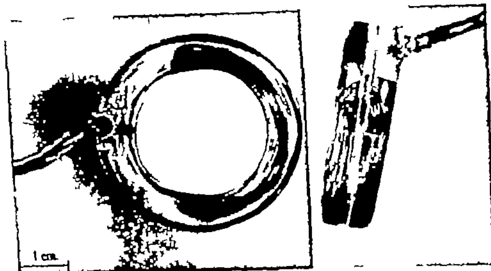


Fig. 1. Mitral valve flow transducer. Top view (left) and side view (right). A fabric fixation ring (not shown) attached to the perimeter of the transducer to facilitate its attachment by sutures.

phase lag was linear with frequency to 18 c.p.s. (3) the damping ratio was 0.23. The flow transducers were used in conjunction with two pulse logic flow meters (Biotronex 610). The static calibration was linear (± 5 per cent) from 0 to 20 000 ml. per minute. The dynamic calibration was as follows: (1) The frequency amplitude response was linear (± 8 per cent) to 50 c.p.s. (2) the phase lag was linear with frequency to 50 c.p.s. The maximum and minimum differences in transit time between the flow and the pressure measuring systems were 2.3 and 1.9 msec. respectively from 1 to 25 c.p.s.

The fractional forward and reverse flows through the mitral valve were obtained by electronic integration of the mitral flow signal using a triggered active integrator. The instantaneous left ventricular volume was measured by passing the mitral and aortic flow signals through a resistive adding network. The resultant algebraic difference was then led into an active integrator.

In the final preparation the following were recorded on magnetic tape (Ampex FR 1300) at 3¾ inches per second: (1) Lead II of the ECG, (2) instantaneous ascending aortic blood flow, (3) instantaneous mitral valve blood flow, and (4) pulsatile aortic, left ventricular, and left atrial pressures.

Aortic regurgitation was produced by

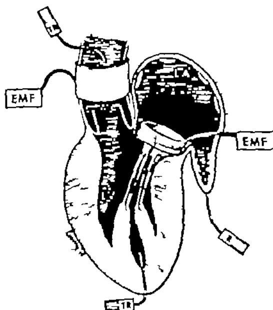


Fig. 2. Diagrammatic representation of the left heart showing the arrangement of the pressure and flow measuring systems. Flow transducers were placed in the left atrium (*LA*) above the mitral valve and on the aorta (*A*). These were connected to electromagnetic flowmeters (*EMF*). Pressure transducers (*TR*) were connected to catheters in the left ventricle (*LV*), LA, and Ao.

passing a nerve hook from the ventricular apex into the aortic root and partially rupturing the noncoronary leaflet of the valve First degree atrioventricular conduction block was produced by the intravenous administration of Prostigmin and when desired this effect was reversed with intravenous atropine Changes in mean left atrial pressure and left ventricular end diastolic pressure were produced by the infusion or withdrawal of blood through a cannula in the right atrium

Each animal was studied for one hour while the aortic valve was normal Aortic regurgitation was then produced and continuous recordings were made for at least two additional hours. During this time the left atrial pressure was varied and atrioventricular conduction block was produced and reversed pharmacologically

Results

Five calves were studied before and after the production of aortic regurgitation In individual animals regurgitant flow through the valve ranged from 32 to 65 per cent of the forward stroke volume and no attempt was made to induce regurgitation of a particular degree of severity

Reverse diastolic mitral gradient High gain recordings of the left atrial and ventricular pressures were made in each animal Prior to the creation of aortic regurgitation a positive atrioventricular pressure gradient developed at the end of protodiastole and persisted until the onset of ventricular contraction After the production of aortic regurgitation the timing of the diastolic mitral gradient varied At heart rates between 90 and 120 per minute and with P R intervals less than 0 18 second the gradient was similar to the normal pattern A reversal of the diastolic atrioventricular pressure gradient was observed in all animals with aortic regurgitation when heart rate was between 90 and 120 per minute and the P R interval was greater than 0 18 second (Fig 3) Reversal of the gradient was also observed in three animals when the heart rate was below 80 per minute but when the P R interval exceeded 0 14 second

The normal pattern of mitral valve flow In the presence of aortic regurgitation and when the heart rate was 90 to 120 per minute and the P R interval less than 0 18 second the pattern of instantaneous mitral valve flow was identical to that observed in normal animals. The six phases of mitral flow[1] were easily identified and they maintained their normal relationship to the atrial and ventricular pressures. Fig 4 illustrates simultaneously recorded pressures and flows in one animal with a heart rate of 110 and a normal P R interval Phase I of mitral flow occurred during protodiastole as the mitral leaflets descended into the ventricle phase II was a period of passive ventricular filling while phase III occurred with atrial systole Phase IV was the only period of reverse mitral flow and its onset was 15 to 20

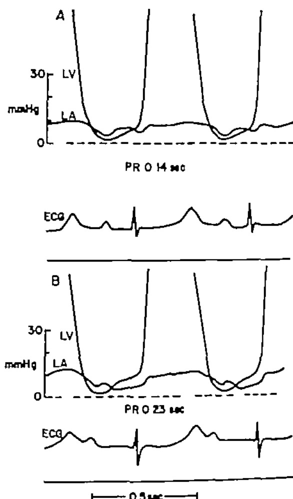


Fig 3 Simultaneous recordings of left atrial (LA) and left ventricular (LV) pressure, and the electrocardiogram (ECG) from calf with aortic regurgitation (heart rate 100 per minute) Top panel (A) was recorded when the P R interval was 0.14 second. The diastolic atrioventricular pressure gradient shows a normal pattern The bottom panel (B) was recorded when the P R interval was 0 23 second. The atrioventricular pressure gradient reversed in mid-diastole.

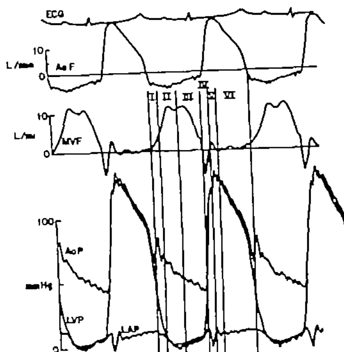
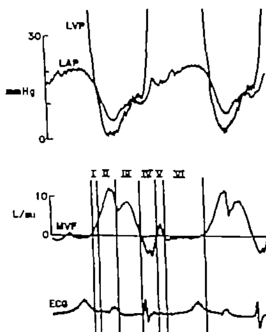


Fig. 4 Simultaneous recordings from calf with aortic regurgitation (heart rate, 103 per minute) and P R interval of 0 15 second Electrocardiogram (*ECG*) aortic blood flow (*A F*) mitral al flow (*MVF*) aortic pressure (*LVP*) and left atrial pressure (*LAP*) The phases of MVF are indicated by Roman numerals. Phases I IV and V have been shaded. The pattern and timing of MVF are normal (see text for description). There as no mitral regurgitation.

Fig. 5 Simultaneous recordings from calf w th aortic regurgitation (heart rate, 92 per minute). The P R interval as 0.20 second. Left ventricular (*LVP*) and left atrial (*LAP*) pressures are shown at the top. With the prolonged P R interval, there as reversal of the LAP LVP pressure gradient during diastole The mitral valve flow (*MVF*) indicates mitral regurgitation (the net sum of the volumes enclosed by phases I IV and V is negative).



msec after reversal of the atrioventricular pressure gradient. Reverse mitral flow continued during the period of in tial ventricu lar contraction and at this time was at tributable to the mitral leaflets bulging into the trium. Phase V was a small volume of forward flow caused by papillary muscle contraction wl ich drew the losed leaflets toward the ventricular apex. Since the sum of the areas enclosed by phases I IV and V was zero there was no net mitral regurgi tation.

Diastolic mitral regurgitation Diastolic

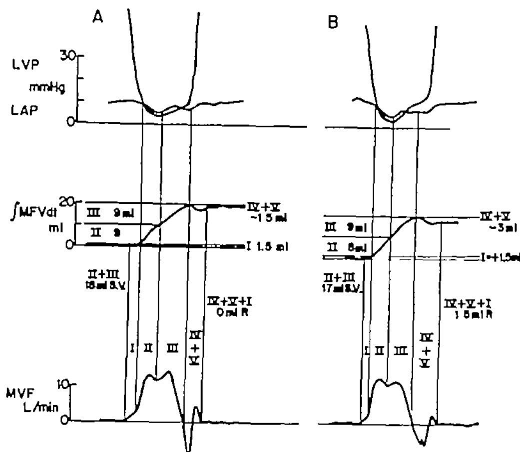


Fig 6 Simultaneous recordings from a calf with aortic regurgitation (heart rate, 98 per minute) Left ventricular (*LVP*) and left atrial (*LAP*) pressure are shown at the top of each panel. The integral of mitral valve flow (*∫ MVF dt*) is shown in the middle and the mitral valve flow (*MVF*) at the bottom The vertical lines indicate the phases of MVF marked in Roman numerals. Horizontal lines have been constructed on the recordings of ∫ MVF dt to indicate the volume of flow during each phase. *Panel A* was recorded with a P R interval of 0.16 second The sum of the integrals of phases I IV and V is zero indicating no regurgitation (*R*) *Panel B* was recorded with a P R interval of 0 23 second. The sum of the integrals of phases II and III shows a stroke volume of 17 ml. The sum of the integrals of phases I IV and V is −1.5 ml. indicating 1.5 ml. R.

mitral regurgitation was defined as any reverse flow occurring prior to ventricular contraction that was greater than the forward flow preceding the onset of the next diastolic period that is the sum of phases I IV and V was less than zero Fig 5 illustrates a typical flow recording of diastolic mitral regurgitation accompanying aortic regurgitation The atrioventricular pressure gradient reversed in late diastole the flow decelerated rapidly and the reverse flow occurred 40 msec. later but prior to ventricular contraction Reverse flow then persisted during initial ventricular contraction and was followed by phase V forward flow The volume of the reverse flow (phase IV) exceeded the sum of the volumes of phases V and I By integrating the instantaneous mitral flow on a beat to-beat basis it was possible to determine the volume of blood exchanged between the atrium and the ventricle during each phase of flow Fig 6 (*A*) shows a normal mitral flow pattern with the simultaneous atrial and ventricular pressures and the integral of mitral flow Phase I had a volume of +1 5 ml. while the combined phases IV and V equalled −1 5 ml There was therefore, no mitral regurgitation Fig 6 (*B*) illustrates a similar recording but with mitral regurgitation Phase I was +1 5 ml and the sum of phases IV and V was −3 0 ml a regurgitant volume of 1 5 ml In these experiments phase IV volumes varied from 2 to 5 ml per stroke and net mitral regurgitation ranged from 1 5 to 4 0 ml per stroke

In three animals with aortic regurgitation heart rate was maintained between 90 and 120 beats per minute and the P R interval was varied from 0 11 to 0 28 second by the intermittent administration of Prostigmin The left ventricular end-diastolic pressure

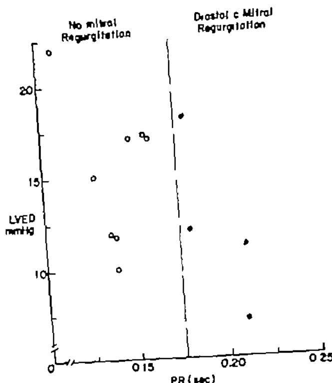


Fig. 7 Graph of the presence (solid circles) or absence (open circles) of mitral regurgitation in the presence of aortic regurgitation at heart rates of 90 to 120 per minute. The left ventricular end-diastolic pressure (LVED) has been plotted on the vertical axis and the P R interval on the horizontal axis. Mitral regurgitation occurred when the P R interval was greater than 0.18 second. There was no apparent relationship between the presence or absence of mitral regurgitation and LVED from 7 to 23 mm. Hg.

was altered independently by the infusion or withdrawal of blood from the right atrium Fig 7 shows the relationship of the P R interval to the left ventricular end diastolic pressure in the presence of aortic regurgitation When the P R interval was greater than 0 18 second, mitral regurgitation was always present, but if the P R interval was less than 0 18 second mitral regurgitation was not observed The measurements were made at levels of left ventricular end-diastolic pressure from 7 to 24 mm Hg but there was no apparent relationship between left ventricular end diastolic pressure and the presence or absence of mitral regurgitation At heart rates below 80 per minute, mitral regurgitation was observed consistently when the P R interval was greater than 0 12 second Fig 8 shows representative patterns of mitral valve flow at P R intervals from 0.08 to 0.22 second. When the heart rate was 65 to 75 per minute (left) the characteristic pattern of mitral regurgitation was found at P R intervals of 0 13 second and greater At heart rates of 110 to 120 per minute (right) the pattern of regurgitation appeared with P R intervals of 0.19 second or more.

Left ventricular volume In three animals the instantaneous left ventricular volume change was assessed in the presence of aortic regurgitation Fig 9 (*A*) is a recording of the left ventricular volume and simultaneous pressure and flow measurements. There was 38 per cent aortic regurgitation but, due to a properly timed atrial contraction there was no mitral regurgitation. Fig 9 (*B*) is a similar recording with distinct mitral regurgitation. The two left ventricular volume curves are quite similar Despite the mitral regurgitation and the cessation of mitral valve flow ventricular volume did not decrease until the onset of ventricular contraction At this point it achieved a plateau and then began to decrease with the onset of forward aortic flow

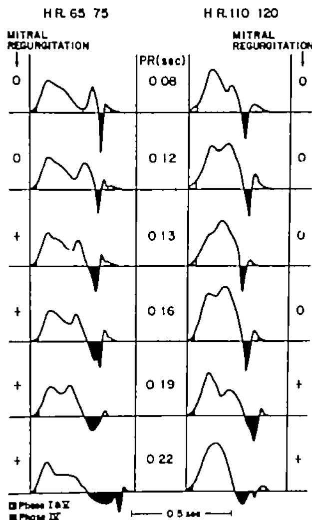


Fig 1 Representative patterns of mitral valve flow in the presence of aortic regurgitation with P R intervals from 0 08 to 0.22 second At heart rates of 65 to 75 per minute (left) mitral regurgitation was present when the P R interval was greater than 0.12 second At heart rates of 110 to 120 per minute (right) mitral regurgitation occurred whe the P R interval was greater than 0.18 second

Discussion

The occurrence of a reversed diastolic mitral gradient in the presence of aortic regurgitation has been reported previously [3,4] These observations, however were made in patients where such factors as the length of the P R interval and the left ventricular end-diastolic pressure could not be varied In patients with aortic regurgitation the P R interval is often longer than normal and it has been suggested that the prolongation serves as a protective mechanism causing early closure of the mitral valve and preventing transmission of the elevated left ventricular diastolic pressure to the pulmonary circuit.[6] In these studies it was shown that diastolic reversal of the atrioventricular pressure gradient occurred with P R intervals greater than 0 18 second and heart rates of 90 to 130 or with P R intervals greater than 0 14 second if the heart rate was 80 or less. Based on these findings and the prolongation of the P R interval in clinical aortic regurgitation it is probable that a reversed diastolic mitral gradient occurs quite frequently in this condition.

The direct recordings of mitral valve flow in the presence of aortic regurgitation demonstrated that mitral regurgitation occurred when there was a reversal of the diastolic pressure gradient across the valve The net fraction of regurgitation observed was only 5 to 19 per cent of the forward stroke volume but this represented a proportional decrease in the efficiency of left atrial transport The effect of mitral regurgitation on atrial muscle mechanics could not be evaluated in these studies. The continuous measurement of ventricular volume change showed that ventricular volume did not decrease until the onset of ventricular contraction Although there was mitral regurgitation during the latter part of diastole the regurgitation of blood from the aorta to the ventricle prevented a decrease in the ventricular volume This would maintain the ventricular myocardium at a maximum level of its length tension curve preventing a decrease in ventricular contractility

From these studies it appears that the mitral regurgitation accompanying aortic regurgitation causes a moderate decrease in the efficiency of atrial transport but has no significant effect on ventricular mechanics. However prolongation of the P R interval is common in patients with aortic regurgitation and it is probable that this results in associated diastolic mitral regurgitation in many of them When preoperative diagnostic studies are carried out in patients with aortic valve disease an important goal is to determine the presence of significant disease of the mitral valve. Unless care is used in the analysis of cineangiograms in these patients mitral regurgitation might be misinterpreted as indicating organic mitral valve disease necessitating operative treatment

Summary

The instantaneous pattern of mitral valve blood flow and the atrioventri ... pressure

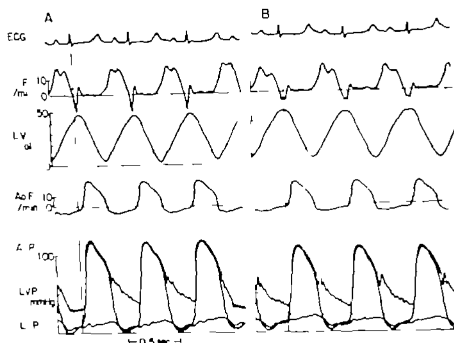


Fig. 9 Continuous left ventricular volume changes (*LV Δ Vol.*) recorded simultaneously with electrocardiogram (*ECG*) mitral valve flow (*MVF*) aortic flow (*A F*) aortic pressure (*A P*) left ventricular pressure (*LVP*) and left atrial pressure (*LAP*). In *A* the P R interval was 0.13 second and the heart rate was 88 per minute. AoF demonstrates aortic regurgitation, but no mitral regurgitation was evident in MVF. *B* was recorded with P R interval of 0.19 second and the heart rate was 108 per minute. MVF shows typical pattern of diastolic mitral regurgitation. In each panel vertical line has been constructed at the onset of ventricular systole. LV Δ Vol. shows that there was no decrease in ventricular volume prior to ventricular contraction in either panel A or panel B (see text for discussion).

gradient were studied in calves before and after induction of acute aortic regurgitation. The timing of atrial contraction, the heart rate, and the left ventricular end-diastolic pressure were varied independently. It was found that in the presence of aortic regurgitation (1) With heart rates of 110 to 120 per minute and P R intervals greater than 0.18 second or with heart rates of 65 to 75 per minute and P R intervals greater than 0.12 second, there was a reversal of the diastolic pressure gradient across the mitral valve. (2) with diastolic reversal of the atrioventricular pressure gradient mitral regurgitation occurred. (3) the occurrence of mitral regurgitation was independent of left ventricular end-diastolic pressure and the volume of regurgitant flow ranged from 5 to 19 per cent of the forward mitral valve flow. (4) due to aortic regurgitation the reversed diastolic mitral flow did not decrease ventricular volume.

The volume of diastolic mitral regurgitation that occurs with aortic regurgitation and an anatomically normal mitral valve is small, and apparently causes no alteration in ventricular volume. Care must be exercised however in the interpretation of left ventricular cineangiocardiograms in patients with aortic regurgitation since diastolic mitral regurgitation might be mistaken for evidence of organic mitral valve disease.

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Case reports

Vascular hamartoma of the heart in a child

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Primary cardiac tumors in children are extremely rare and in the majority of reported cases the diagnosis has been made post mortem[1,2] The vast majority are benign histologically with only one or two of the half dozen reported malignant tumors in children being accepted by various authorities[2,3] We recently had the opportunity to study in detail including biopsies, a peculiar angiomatous tumor of the heart in an 8½ year-old girl The case is being reported with the hope that documentation of such rare entities may shed light on their true incidence and natural history

Case report

M T is an 8¼-yea -old Caucasian girl who was admitted, on July 21 1967 to the Naval Hospital Bethesda Md from the Naval Hospital Charleston, S. C. for cardiac catheterization. She was apparently in excellent health, with normal growth and development, until two years prior to admission when cardiomegaly was noted on a chest x ray taken during an episode of 'bronchitis. The electrocardiogram at that time was nterpreted as demonstrating 'left ventricular enlargement with train pattern. She was thought to have endocardial



Fig *1* Chest x ray on admission.

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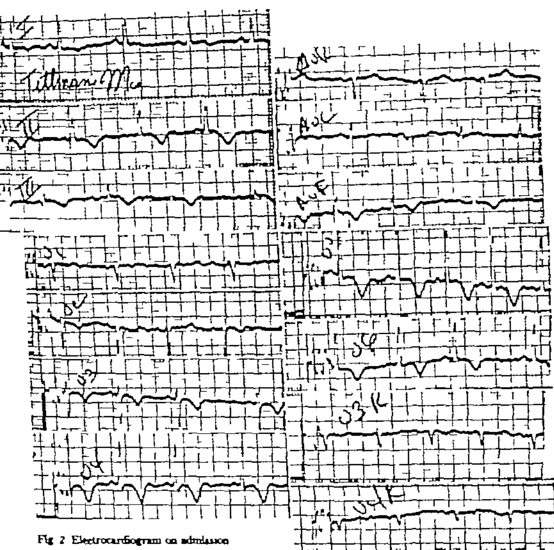


Fig. 2. Electrocardiogram on admission.

fibroelastoma, and digoxin therapy 0.25 mg. per day was instituted. Neither prior to nor since that time has she manifested any signs of congestive heart failure.

The patient was first seen in the Cardiology Clinic, Naval Hospital, Bethesda, in January, 1966. She was followed closely and maintained on digoxin until slight decrease in exercise tolerance and further enlargement of the cardiac silhouette on chest x-ray prompted admission for further evaluation, on July 21, 1967.

Physical examination on admission to Bethesda Naval Hospital revealed a well-nourished, well-developed female, weighing 28 kilograms. Blood pressure was 110/70 in the upper arm and the pulse was 90 per minute and regular. The pertinent physical findings were limited to the heart. The border of cardiac dullness extended to the left anterior axillary line. The first and second heart sounds were normal and neither cardiac murmurs nor bruits were heard. The peripheral pulses were normal. The remainder of the physical examination was within normal limits including the absence of hemangiomas of the skin or buccal mucosa.

Laboratory studies included 13 Gm. per 100 ml. hemoglobin and 7,500 white blood cell count per cubic millimeter with normal differential. Urinalyses, serum electrolytes, and liver battery including total protein, bilirubin, alkaline phosphatase, and serum glutamic oxalacetic transaminase, were within normal limits. Latex fixation and antistreptolysin-O titer studies were normal. Skin tests for tuberculosis, histoplasmosis, and coccidioidomycosis were negative. Chest x-rays, including



Fig 3 Cineangiogram showing tortuous left anterior descending coronary artery (to the right) Also noted are an increased number of slowly emptying vessels over the apex.



Fig 4 Chest x ray following pericardiocentesis.

cardiac series, demonstrated gross enlargement of the cardiac silhouette in a rounded configuration (Fig 1) The electrocardiogram showed an axis deviation of plus 30 degrees, with diffuse deep inversion of the T waves compatible with myocardial disease (Fig 2)

On July 25 1967 right and left cardiac catheterization with cineangiography was performed. Pressures in the right side were normal and did not suggest cardiac tamponade. Left ventricular end-diastolic pressure after mild exercise was 24 mm. Hg. Oxygenation determinations of blood samples indicated no evidence of shunts. On cineangiography there were neither atrial nor ventricular filling defects. The anterior descending coronary artery branches were dilated and tortuous, and the apex contained an increased number of arterial branches which emptied slowly (Fig 3) The size of the space between the coronary arteries and outer limits of the cardiac silhouette suggested pericardial effusion.

On July 26, pericardiocentesis removed 600 ml. of straw-colored fluid Chest x rays (Fig. 4) taken following instillation of carbon dioxide and air into the pericardial cavity demonstrated no pericardial thickening Viral bacterial, fungal and cytological studies of the pericardial fluid were negative.

Exploratory thoracotomy was performed on Sept. 8 1967 and a large anterior pericardial window was made, after aspirating 300 ml. of clear straw colored pericardial fluid. The heart was moderately enlarged and the left anterior descending coronary artery branches were markedly dilated and tortuous. The entire apex of the heart, including both ventricular surfaces, was covered by a light grey fibrotic mass with focal nodularity which extended into the myocardium (Fig. 5) The superior border zone, between the tissue mass and normal appearing epicardium and myocardium, was reddened. There was no thrill palpable over the tumor Resection of the entire tumor was not considered feasible and biopsies were taken.

The child s postoperative course was satisfactory and she was discharged on Sept. 22, 1967 The parents were informed that the prognosis was guarded, but that she bould be allowed to continue her physical activities to tolerance. She is presently being mai tained on digoxin 0.25 mg per day and has been free of symptoms for 18 months following surgery

Histology

Three small fragments of tissue were received measuring 6 by 3 by 1 mm 3 by 2 by 1 mm., and 5 by 3 by 2 mm., respectively along w th a portion of pericard um. One of the biopsy specimens, on multiple sectioning, consisted only of blood clot.

Multiple sections of the remaining two biopsies were stained with hematoxylin nd eosin. In addition special stains ncluding Masson s trichrome, Mo at pentachrome, Verhoeff elastic, Gomori's reticulum iron, and periodic acid Schiff were utilized

The biopsies were of similar histology The subepicardial connective tissue contained focal collagenization accou ting for the nodularity noted grossly In add tion, there was a diffuse perivascular fibrosis and the coronary blood vessels were increased i number and structurally abnormal. The vessels showed thickened media and focal intimal thickening by fibromyxomatous tissue. Most of these vessels did not demonstrate an internal elastic lamina. The underlying myocardium was infiltrated by a striking diffuse interst tial proliferation of



Fig. 5. Anterior view of heart showing white discoloration and focal nodularity over the apex. The sutures represent biopsy sites.

small vascular channels without muscular walls and lined by plump endothelial cells (Figs. 6 and 7). Neither luminal proliferation of endothelial cells nor perivascular proliferation of pericytes was noted. The luminal diameter of these vessels was quite small and their histologic appearance was capillary or venular. Accompanying and surrounding these vessels was dense, relatively acellular fibrous connective tissue containing a few scattered mononuclear inflammatory cells and foci of adipose tissue. There are several vessels with well-defined medial smooth muscle. The intervening myocardial fibers are moderately hypertrophied and arranged haphazardly. Occasional myocardial fibers demonstrated early nonspecific degenerative changes. Abundant granular brown pigment was present, both free in the interstitial tissue and within the sarcoplasm of many myocardial fibers. The pigment turned positive for iron. There was no histologic evidence of malignant alteration.

The pericardium was thickened by dense, collagen fibers containing focal lymphocytic aggregates. Moderate lymphangiectasia and vascular congestion are evident.

Discussion

The incidence of primary cardiac tumors in autopsy studies is approximately 1 per 10,000 in patients of all ages[1,4] and is far less in infants and children. Two cardiac tumors that occur most frequently in infants and children are the rhabdomyoma and fibroma.[3,7,11] The fibroma is frequently focally calcified and is characteristically intramural, involving predominantly the interventricular septum or wall of the left ventricle. The rhabdomyoma can be single or multiple; the latter is noted predominantly in young *infants with tuberous sclerosis*. The discussion as to the neoplastic or hamartomatous nature of these lesions remains unsettled.

Primary hemangiomatous tumors of the heart are extremely rare.[11,7] The exact incidence is unknown, being complicated by uncertainty in the literature as to whether some of these lesions represent varices or true hemangiomas. Most reported hemangiomas have been small, subendocardial in location, and seemingly lacked infiltrative features. The cardiac tumor described in this report has been simply classified as a vascular hamartoma. The histologic appearance and clinical course suggest a *hamartoma rather than a* neoplasm.

Timmes and associates[16] reported a somewhat similar case in a 10-year-old girl; however, detailed written and photographic descriptions of the pathologic findings were

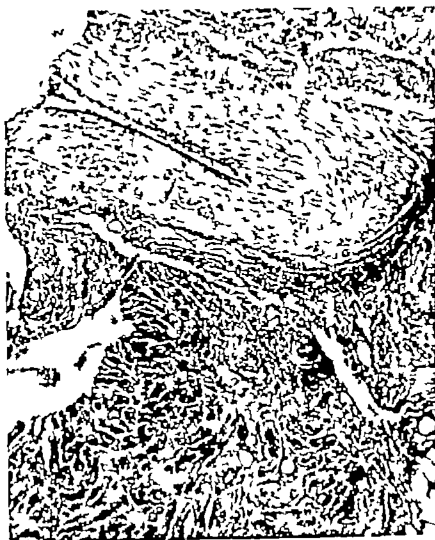


Fig 6. Large coronary vessel w thin the ep card um (top) and many small vascular channels and fibrosis (×125)

not presented That lesion was also unresectable and the patient was treated with radiation She was apparently well seven years after therapy

May and associates[13] reported resection of a 6 5 cm cystic vascular hamartoma from the right atrium of a 10 year-old boy The lesion was apparently chiefly epicardial however resection of a portion of the atrial wall was technically required It was composed primarily of cavernous vascular spaces surrounded by dense fibrous connective tissue which contained randomly arranged smooth muscle fibers Actual myocardial permeation was not described

There is striking histologic similarity between benign angiomatous tumors of skeletal muscle (hemangiomas in skeletal muscle)[17 18] and the tumor we have reported The skeletal muscle angiomas have been considered congenital in origin since most occur in the first decade Histologically they are hamartomas and characteristically they have indolent courses however ultimately they are locally aggressive and seemingly cured only by total excision Sclerosing solutions and radiation have been only temporizing measures. If the cardiac tumor we have reported is similar to the angiomatous tumors of skeletal muscle the long term prognosis would be poor Hopefully close follow up will provide clues to help guide future evaluation and therapy in similar cases.

In the recent past the diagnosis of cardiac tumors was primarily at post mortem examination The recent advances in cardiac catheterization cineangiography and cardiac surgery have placed a burden



Fig. Multiple small vascular channels and fibrosis dispersed between myocardial fibers (×400)

upon the physician to detect primary cardiac tumors ante mortem. Unfortunately the clinical signs produced by such tumors are nonspecific and more often associated with common entities, e.g. pericarditis and rheumatic heart disease. In general the clinical signs are dependent on the anatomical location of the tumor[1,2] i.e. pericardial effusion associated with pericardial tumors, cardiac arrhythmias with intramural tumors, valvular stenosis or insufficiency and tumor emboli associated with intracavitary tumors.

Summary

An 8½-year-old Caucasian girl is described who presented with pericardial effusion. Cineangiography demonstrated a vascular cardiac tumor which was biopsied. The tumor was considered histologically to be a vascular hamartoma composed of small blood vessels. The patient remains well one year following surgery; however, the prognosis is uncertain.

We would like to acknowledge the helpful comments and guidance provided by William C. Manion, M.D., Chief of the Cardiovascular Pathology Branch at the Armed Forces Institute of Pathology, Washington, D. C.

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False positive ECG response to exercise secondary to hyperventilation: Cineangiographic correlation

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Hyperventilation can cause S-T–segment and T wave changes simulating myocardial ischemia in individuals free of clinical heart disease[1] resulting in a false positive S-T–segment response to exercise. Although this observation is familiar to those involved in exercise testing, it is uncommon, and objective cineangiographic confirmation of the absence of coronary artery disease in an individual manifesting this phenomenon has not been hitherto reported. The purpose of this paper is (1) to describe a patient with a false positive S-T–segment response to treadmill exercise due to hyperventilation in the presence of normal coronaries as delineated by cineangiographic studies and (2) to outline the behavior of the S-T–segment changes with exercise which might lead one to suspect a false positive response due to hyperventilation rather than true organic S-T–segment alterations.

Case report

The patient, R. L. H. (No. 445388), 30-year-old Caucasian male laborer, was referred to the Indiana University Medical Center for evaluation of precordial chest pain of 2 months' duration. The patient described the pain as being "sharp, aching," localized to the precordium, at times associated with shortness-of-breath, dizziness, palpitations, diaphoresis, and weakness. The pain occurred at rest as well as with exertion and frequently occurred during periods of anxiety or emotional distress. The patient had been awakened at night by the pain on several occasions. The pain would usually subside within 15 minutes. The past medical history revealed that the patient had been hospitalized two times in the preceding 2 years for right lower quadrant pain for which no cause could be found. The family history was not contributory.

Physical examination revealed a blood pressure of 110/70 mm. Hg and a heart rate of 79 beats per minute. The remainder of the examination was within normal limits.

The resting electrocardiogram (ECG) (Fig. 1) showed a minor terminal intraventricular conduction defect and low amplitude T waves in Leads II, III, and V. Roentgenographic studies of the

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Table I. Staging program for treadmill exercise test

Stage	Speed (m p h)	Grade (%)	Time (min)
I	2 0	3	3
II	3 3	6	3
III	3 3	9	3
IV	3 3	12	3
V	3 3	15	3
VI	3 3	18	3
VII	3 3	21	3

chest upper and lower gastrointestinal tract, including a barium swallow and gall bladder were within normal limits. The complete blood count, urinalysis, blood urea nitrogen, and serum electrolytes, including serum calcium were within normal limits. The total serum lipids and 2 hour post prandial blood sugar were also normal.

Treadmill exercise testing was performed in the fasting state using the staging program outlined in Table I. The exercise ECG's were recorded with a bipolar V_5 (C5R C5) electrode system. The effect of hyperventilation was studied on 2 consecutive days and ECG's were recorded using the same electrode reference system.

Selective coronary cineangiography was performed by the percutaneous femoral approach. The

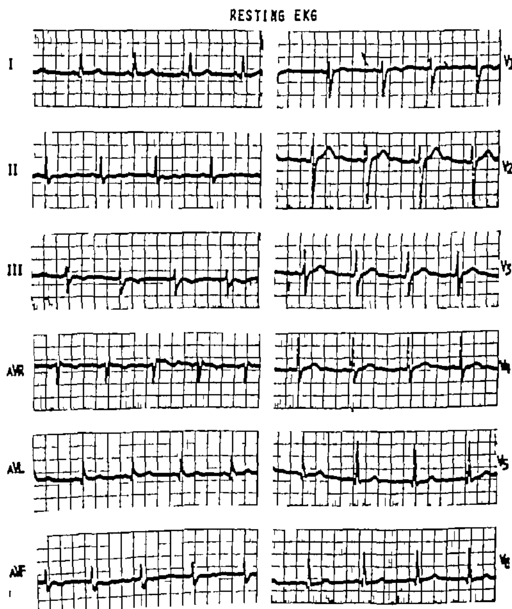


Fig. 1. Resting 12 lead ECG taken on Oct. 27, 1968 showing a minor terminal intraventricular conduction defect and low amplitude T waves in Leads II, III and aVF.

filming was done on a 6 inch Phillips image intensifier with 100 mm. overframing lens. Injections were done in multiple oblique views with and without nitroglycerin.

The patient exercised on the treadmill for 14 minutes (Stage V) and attained a heart rate of 176 beats per minute without experiencing chest pain. The exercise was terminated short of maximal effort when the patient experienced dizziness and became unsteady. He stated that the dizziness was similar to that he experienced during episodes of chest pain. There was no drop in the blood pressure during or after exercise.

One millimeter of segmental S-T-segment depression was first noted early in Stage II of exercise and maximal S-T depression was present at the start of Stage III (Fig. 2). During the last two stages of exercise (Stages IV and V), the S-T segment became less horizontal, but there was no change in the magnitude of J junction depression. The immediate postexercise record was similar to the maximal exercise record but segmental S-T depression reappeared within 2 minutes after cessation of exercise.

In each instance voluntary hyperventilation for 20 seconds resulted in 1 mm. or more of segmental S-T depression which persisted for 20 seconds after cessation of hyperventilation (Fig. 3).

Selective coronary cineangiography failed to

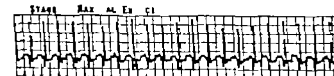
MAXIMUM TREADMILL EXERCISE TEST













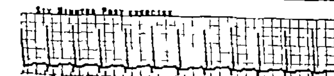


Fig. 2. Bipolar V5 Lead, taken on Oct. 31, 1968, showing segmental S-T depression during and after exercise.

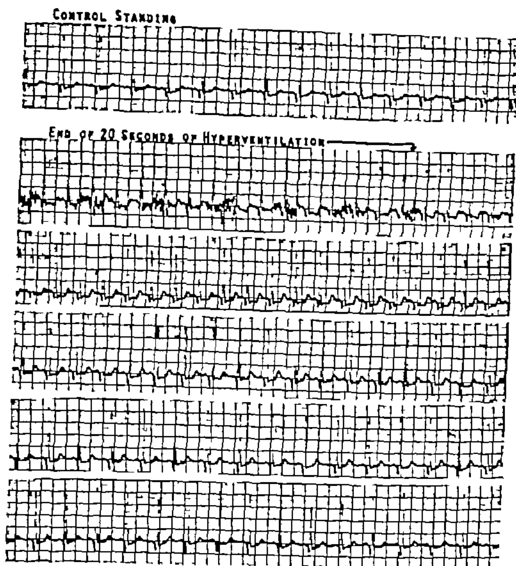


Fig 3 Bipolar V Lead taken on Oct. 31 1968, showing segmental S-T depression during and after voluntary hyperventilation All strips except the top one, represent a continuous tracing

show any evidence of coronary artery disease. Right heart and left ventricular pressures were normal and the left ventricular cavity appeared normal in size and shape on a ventriculogram

Discussion

This patient with atypical chest pain demonstrated segmental S-T–segment depression during and after treadmill exercise a finding usually associated with ischemic heart disease However the lack of clinical and laboratory evidence of heart disease including coronary cineangiography and the ability to reproduce the S-T–segment changes with hyperventilation indicates that the electrocardiographic changes represented a false positive response to exercise.

Segmental S-T–segment depression during strenuous exercise due to hyperventilation and not organic heart disease is uncommon We have observed 3 individuals with this phenomenon and all have had certain electrocardiographic features in common The segmental S-T depression appeared very early in the course of exercise usually within the first 3 minutes, in the absence of any symptoms. The maximal S-T–segment depression was also observed early during exercise in contrast to the progressive increase in magnitude of J or S-T depression usually seen in both normal subjects and patients with cardiac disease with increasing work loads.[1] These 3 individuals continued to exercise beyond the time of appearance of segmental S-T depression and in 2 of them the horizontal

contour of the S-T segment became less prominent as they approached their maximal exercise capacity. However segmental S-T depression has always reappeared after the termination of exercise and persisted for 6 minutes or more. In all 3 subjects the S-T-segment depression observed during exercise could be reproduced with 20 seconds or less of hyperventilation.

Our observations and those of other investigators indicate that all patients manifesting a positive S-T-segment response to exercise should also be studied during hyperventilation to rule out false positive responses.[4] Of course, the ability to reproduce segmental S-T depression with hyperventilation does not exclude the possibility of underlying heart disease, and the total clinical and laboratory picture must be considered in the final interpretation of an abnormal response to exercise. Even if the segmental S-T-segment changes cannot be reproduced with hyperventilation other entities which can cause a false positive response to exercise such as hypokalemia and digitalis must be considered.

Summary

A patient with atypical precordial chest pain demonstrated segmental S-T-segment depression in response to treadmill exercise. Although this finding was very suggestive of the presence of ischemic heart disease the reproducibility of these S-T-segment changes with hyperventilation and a normal coronary cineangiographic study supported our impression of a false positive response to exercise.

Certain characteristic electrocardiographic features observed in patients manifesting a false positive response to exercise due to hyperventilation are described.

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Aneurysm of the pars membranacea

Report of three adult cases and a review of the literature

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The interventricular septum is divided into two components the pars muscularis and the pars membranacea. The greater portion of the interventricular septum is the thick and muscular pars muscularis which separates the two ventricles. Aneurysms of this muscular portion of the interventricular septum are almost always acquired after myocardial infarction[1-4] though rarely they may be congenital.[5] At the upper and posterior margins of the muscular septum is located a relatively small thin oval shaped fibrous structure which separates the aortic vestibule from the lower part of the right atrium and the upper part of the right ventricle. This is the pars membranacea.[6] The inferior margin of this membranous septum is adjacent to the muscular septum at its posterior attachment the pars membranacea is in close proximity to the bundle of His.

The clinical significance of the pars membranacea is that it is the most common site for congenital interventricular septal defects[7] which because of the septum's anatomical location may also give rise to a congenital communication between the left ventricle and the right atrium.[8]

Aneurysm of the membranous septum is another though less common lesion of the membranous septum. The purpose of this communication is to present three adult patients with membranous septum aneurysm and to review the literature on this subject.

Case reports

Patient 1 A 65-year-old housewife had a heart murmur noted at the age of 30 but was entirely asympt matic until two years before admission when she noted mild orthopnea and dyspnea. Her symptoms were adequately controlled with medication. The patient entered the hospital for cardiac catheterization. Physical examination disclosed blood pressure 120/80 mm Hg and pulse rate 84 per t. Arterial and jugular enous pulses were normal. Precordial palpation revealed a systolic thrill o er the lower left ternal border. A Grade 4/6 harsh pa s tolic murmur was heard along the lower left sternal border. The second sound was normally pl t. The rema nder of the physical examination was normal. The lectrocardiogram and ectorcardiogram were normal.

Chest roentgenogram showed normal pulmonary scular markings. The transverse diameter of the heart was slightly enlarged. A calcified aortic knob w noted to the right of the midline.

Cardiac catheterization (Table I) revealed a left to-right sh t at the ventricular level. Position g a platinum tip catheter in arious parts of the right heart and utilizing ascorbic acid injections[9]

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Table I

Study	*Patient 1*	*Patient 2*	*Patient 3*
Pressures (mm. Hg)*			
Aorta	133/64 (105)	104/53 (70)	108/46 (64)
Left ventricle	126/10	94/11	108/8
Pulmonary "capillary" wedge	(4)	(6)	(7)
Pulmonary artery	22/8 (10)	22/8 (13)	23/10 (14)
Right ventricle	21/1	21/5	23/2
Right atrium	(1)	(3)	(0)
Oxygen consumption (ml./min./M.²)	145	158	146
Flow indices (L./min./M.²)			
Pulmonary	6 66	4 27	5 68
Systemic	3 33	3 15	3 22
Left-to-right shunt	3 33	1 12	2 46
Pulmonary systemic flow ratio	2 0:1	1 4:1	1 8:1
Resistances (dynes/sec./cm.⁻⁵)			
Systemic	1720	960	1135
Pulmonary	45	74	106
Shunt work-up†			
Blood oxygen step-up in right ventricle	+	+	+
Hydrogen	+	+	+
Ascorbic acid	+	—	—
Dye dilution curves	—	+	—

*Mean in parentheses = mean pressure.
†+ indicates an interventricular shunt detected by this method and — indicates technique not performed.

into the left ventricle and hydrogen inhalation[14] localized the shunt at the ventricular level. Multiple blood samples obtained from the right heart demonstrated a significant step-up of oxygen content at the right ventricular outflow tract. A retrograde catheter entered the left ventricle, a right descending and right aortic arch.

Biplane angiography performed following injection of contrast material into the left ventricle revealed a globular-shaped structure with a somewhat narrow base projecting from the left ventricle into the right ventricular outflow tract (Fig. 1). Contrast material was noted streaming from the inferior aspect of this globular structure resulting in opacification of the right ventricular outflow tract.

Comments. The unusual feature of this case is the age of the patient and the finding of a right-sided aortic arch.

Patient 2. A 39-year-old Negro woman was admitted for cardiac catheterization because of a heart murmur. The patient had known of a heart murmur since the age of twenty but had been asymptomatic. Physical examination revealed a blood pressure of 110/70 mm. Hg and a regular pulse rate of 80 per minute. Pertinent findings were limited to the heart. A harsh pansystolic Grade 5/6 murmur accompanied by a thrill was heard along the lower left sternal border. The second sound was normally split. No gallops were heard. The electrocardiogram and vectorcardiogram were normal. The chest roentgenogram revealed both normal pulmonary vascular markings and heart size.

Cardiac catheterization (Table I) revealed a left-to-right shunt at the ventricular level. The localization of the shunt was demonstrated by multiple blood oxygen determinations, dye dilution procedures, and a platinum-tip catheter with hydrogen inhalation.

A biplane angiogram was made following injection of contrast material into the left ventricle. This revealed (Fig. 2) a sharply defined aneurysm high in the ventricular septum protruding into the right ventricular outflow tract. Contrast material was noted streaming from the apex of the aneurysm into the right ventricle.

Patient 3. A 72-year-old Caucasian woman was admitted to the hospital for treatment of acute glaucoma. While in the hospital the patient was seen by the cardiology service because of a heart murmur. The patient had known of a heart murmur since she was a child but never sought any medical advice. She had no history of rheumatic fever, anginal pain, dyspnea, orthopnea, or pedal edema. Because of the uncertain etiology of the heart murmur the patient consented to a diagnostic cardiac catheterization. Physical examination showed a blood pressure of 110/70 mm. Hg and a pulse rate of 80 per minute. Significant findings were limited to the heart. The heart was not enlarged to percussion or palpation. The first sound was of normal intensity. A systolic thrill was felt at the lower left sternal border. A Grade 3/6 harsh pansystolic murmur was heard over the apex, radiating to the left sternal border and the base. No gallops were heard.

The electrocardiogram showed abnormal left axis deviation but was otherwise within normal limits. The vectorcardiogram demonstrated only a superior counterclockwise frontal loop.



Fig 1 Patient 1 A Retrograde catheter (arrow) demonstrating course of right side aortic arch and descending aorta. Note also aortic knob calcification to the right of the spine. B Early lateral phase of angiogram with contrast material in the left ventricle. Membranous septum aneurysm (upper arrow) with jet of dye (lower arrow) from the inferior aspect of the aneurysm entering the right ventricular outflow tract. C Later phase of angiogram now showing opacification of the aorta (*AO*). A jet of dye (unmarked arrow) from the membranous septal aneurysm (*AN*) opacifying the right ventricular outflow tract (*RV*) and main pulmonary artery (*MPA*).



Fig. 2. Patient 2. *A*, Frontal view showing the aneurysm (unmarked *arrow*) *projecting as a slight bulge high* up on the ventricular septum. *B*, Lateral projection with a transseptal catheter positioned in the left ventricle (*LV*). A well-defined globular aneurysm (*A*) is demonstrated with dye entering the right ventricular outflow tract (*RV*) and opacifying the main pulmonary artery (*MPA*). Note the jet of dye (unmarked arrow) at the apex of the aneurysm.

The chest roentgenogram revealed normal pulmonary vascular markings. The heart size was normal.

Cardiac catheterization (Table I) demonstrated left-to-right shunt at the ventricular level. A biplane angiogram was made with injection of contrast material into the left ventricle (Fig. 3). This revealed an aneurysmal bulge high up on the membranous septum with dye streaming into the right ventricular outflow tract from the inferior aspect of the aneurysm.

COMMENT. This case and the previous case illustrate the benign course this lesion may have. Patient 3 is the oldest living patient with aneurysm of the pars membranacea.

Discussion

Embryology. The membranous septum develops during the seventh and eighth week of gestation and is the last portion of the interventricular septum to form. After completion of the muscular part of the interventricular septum an interventricular foramen is still present which is destined to be closed by the pars membranacea. This foramen is bounded superiorly by the spirally directed fused truncoconal septum which extends anteriorly and is joined to the muscular interventricular septum. The muscular septum forms the concave inferior margin of the foramen. The posterior aspect of the interventricular foramen is formed by the right tubercles of the anterior and posterior endocardial cushions which fuse superiorly to the truncoconal septum and inferiorly to the muscular septum.[11, 12] The interventricular foramen is closed with formation of the pars membranacea, by the growth downward of the caudal ends of the truncoconal septum fusing with tissue proliferation from the endocardial tissue and from connective tissue arising from the superior margin of the muscular interventricular septum.[11-13, 14]

Anatomy. As viewed from the left ventricle (Fig. 4) the superior border of the pars membranacea is attached at the

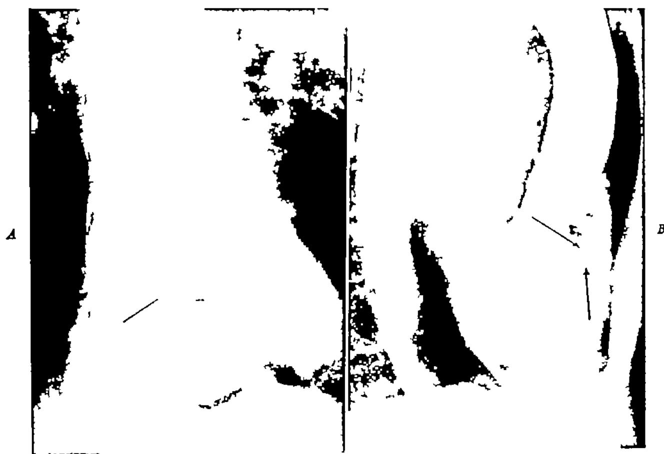


Fig 3 Patient 3 A Frontal projection with the aneurysm (unmarked arrow) presenting a localized bulge high up on the ventricular septum B Lateral projection revealing an aneurysm (upper arrow) extending anterior a a globular tructure with d e (lower arrow) tream ng fr t inferior urface

angle between the edges of the right and posterior aortic valve As viewed from the right side (Fig 5 A) the membranous septum is partly concealed by the septal cusp of the tricuspid valve which is attached across it diagonally Therefore that portion which is above the attachment of the tricuspid valve forms a partition between the right atrium and left ventricle while the larger portion located below the attachment of the tricuspid valve separates the right ventricle from the left ventricle The posterior margin of the membranous septum is attached to the right fibrous trigone which serves as a supportive framework of the heart and to which also the anterior leaflet of the mitral valve is partially attached

Pathogenesis According to Lev and Saphir[13] an embryologic basis for the formation of a membranous septum aneurysm may be explained by either a defective formation of the endocardial cushion or an abnormality in the fusion of the caudal ends of the truncoconal septum and the muscular ventricular septum The latter explanation first proposed by Mall[11] was favored by Lev and Saphir Mall noted in his case that the membranous septum instead of extending directly upward was directed to the right in a somewhat horizontal plane to join the right side of the root of the aorta The normal development of the aorta requires it to shift toward the left resulting in an alignment of the right side almost vertical to the membranous septum Failure of this shift would thus cause a more horizontal position of the membranous septum in essence a partial transposition would be present resulting in an abnormally oriented membranous septum It is interesting that cases of membranous septum aneurysm associated with corrected and complete transposition of the great vessels have been reported[13,14] Mall felt that this abnormal attachment of the membranous septum caused inherent weakness and made it prone to bulge to

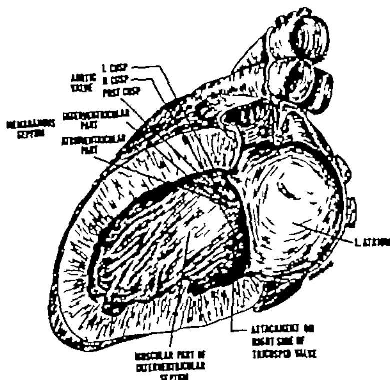


Fig. 4. *The interventricular septum as viewed from the left ventricle.* The major portion of the septum is the muscular part. The membranous septum is seen high up on the interventricular septum being immediately below the posterior (noncoronary) and right aortic cusp. Stippled line indicates the attachment of the septal leaflet of the tricuspid valve on the right side. Note that inferior to the attachment of the tricuspid valve is the atrioventricular part of the membranous septum whereas superior to this attachment is the interventricular part of the membranous septum. Therefore, the membranous septum separates the left ventricle from both the right atrium and right ventricle.

the right from the higher left ventricular pressures. Mall's anatomical observations have been noted by other authors,[12, 13, 7] but have not been recently confirmed by Baron and associates. Abnormalities in the fusion of the endocardial cushion have been considered by other authors as a possible explanation for a membranous septum aneurysm,[19, 20] whereas Sakakibara and Konno[21] favored *inadequate fusion of the truncoconal septum* to explain not only the morphogenesis of the membranous septum aneurysm but also an aneurysm of the sinus of Valsalva. The association of Down's syndrome with both membranous *septum* aneurysm[13, 14, 22] and defects of the atrioventricular canal[23] would favor a role for an endocardial cushion abnormality in the formation of a membranous septum aneurysm. Other explanations proposed for the formation of a *membranous* septum aneurysm include endocarditis and abnormalities of the tricuspid valve.[23]

The most recent explanation proposed to explain formation of a membranous septal aneurysm is that it results from a previous spontaneously closed ventricular septal defect and a high left ventricular pressure which causes bulging to the right of an intrinsically weak membranous *septum*.[14, 24] *Adherence of the septal leaflet* of the tricuspid valve to a membranous septal defect has been described as one of the mechanisms for spontaneous closure of a ventricular septal defect.[24] The high left ventricular pressure may thus cause *bulging of this* attached portion of the septal leaflet into the right atrium (Fig. 5 *B* and *C*). Therefore in this situation there is really not a membranous septal aneurysm but rather a pouch of the septal leaflet of the tricuspid valve. This may be impossible to distinguish from a true membranous

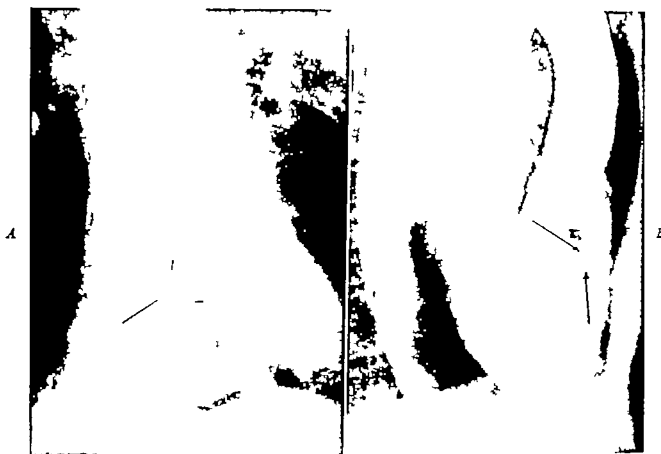


Fig 3 Patient 3 A Frontal projection with the aneurysm (unmarked arrow) presenting as a localized bulge high up on the ventricular septum B Lateral projection revealing an aneurysm (upper arrow) extending anterior as a globular structure with dye (lower arrow) streaming from its inferior surface.

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cal closure, a repeat angiogram performed because of the persistence of a murmur and a thrill, demonstrated a membranous septal aneurysm and a small residual defect. Baron and associates also described the same sequence of events in one of their cases. These two cases document an acquired membranous septal aneurysm and would suggest that such aneurysm formation is related to weakening of the membranous septum associated with inadequate closure of the defect. Furthermore it would support the theory that these aneurysms are acquired and result from inherent weakness of a spontaneously fibrous closure of a ventricular septal defect.

Clinical aspects. According to Lev and Saphir[illegible] a membranous septal aneurysm was first described by Laennec in 1826.[19] During the next 112 years there were approximately 70 cases described in the world literature.[illegible] Membranous septal aneurysm is a rare lesion. The combined autopsy series of Rae[illegible] and Steinberg[illegible] revealed only 6 cases in 19,000 autopsies, and in 1,000 cases of congenital heart disease reviewed by Abbott[illegible] there were 16 cases. Steinberg[illegible] in 1957 reported the *first case diagnosed in a living patient by* angiocardiographic methods and could find a total of 80 cases reported in the literature. Since then there have been at least an additional 56 cases described in the literature.[illegible] Therefore a total of at least 136 cases have been described, the diagnosis being made at autopsy in 98 by angiocardiography in 27 and at surgery in 11 patients. The lesion has been found in all age groups with the youngest patient being 3 weeks old[illegible] and the oldest, 72 years old.[19] Both of these patients had the diagnosis made at autopsy. Patient 3 of the present series is the oldest patient having this diagnosis made while alive. Although all the patients in the present series are female, the sex distribution as found in the literature has been equal.

A membranous septal aneurysm may occur as an isolated defect,[illegible] the diagnosis usually made as an incidental finding at postmortem examination. Only rarely has the diagnosis been made clinically *in similar* circumstances and in these cases angiocardiography was performed because of a heart murmur[illegible] or surgery performed because of an abnormal mass in the cardiac shadow.[44]

Most cases with membranous septal aneurysm have been associated with a congenital cardiac defect (Table II). The most frequent lesion found was a *ventricular* septal defect located in the aneurysm itself usually associated with a relatively small left-to-right shunt. This was the case with our 3 patients in the present report. Moncada and associates[41] reported two cases of membranous septal aneurysm in 22 children with membranous ventricular defects. We have catheterized 15 adult patients (mean age 36) with a membranous septal defect and have found an associated membranous septal aneurysm in 3 cases. The 10 per cent frequency found in the pediatric age group as compared to the 20 per cent incidence in the adult population would suggest that this lesion may be acquired in nature.

The aneurysm may protrude inferior to the tricuspid valve (Fig. 5, *E*) and bulge into the right ventricle.[illegible] In some cases, the aneurysm expands with systole into the right ventricular outflow tract and causes right ventricular outflow *obstruction.*[illegible] *In this situation a* clinical diagnosis of infundibular pulmonic stenosis may be made, the correct diagnosis forthcoming only at surgery.[illegible] The aneurysm (Fig. 5, *E*) may also bulge directly into or attach itself to the septal leaflet of the tricuspid valve[illegible] or protrude at the base of the attachment of the leaflet to the tricuspid annulus.[illegible] Occasionally the pouch can *protrude from its* right ventricular aspect into the tricuspid ostium and encroach on its orifice.[illegible] An associated systolic murmur in such a case was attributed to the production of tricuspid insufficiency.[illegible] When the aneurysm bulges at a point superior to the tricuspid valve (Fig. 5, *D*) it will project into the right atrium.[illegible] In three exceptional cases the aneurysm presented itself exterior to the heart.[illegible] In two cases[illegible] the aneurysm extended from below the base of the aortic valve ring over the anterior surface of the heart, while in the third case[illegible] it bulged behind the ascending aorta and extended between the pulmonary artery and the left atrium. In two of the cases the diagnosis was made at autopsy[illegible] while in

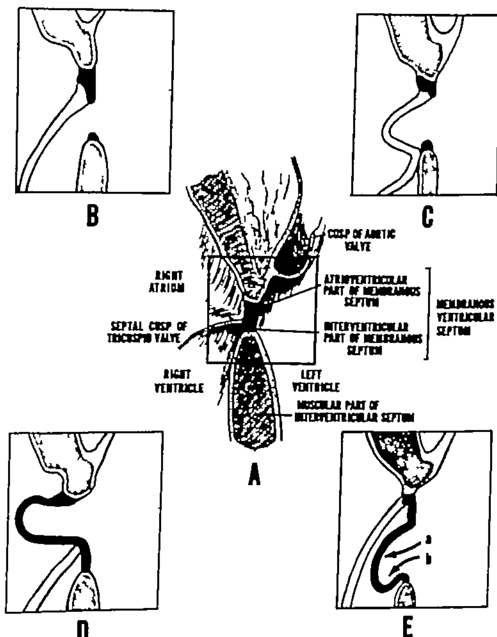


Fig 5 *A* Projection through the membranous septum showing the atrioventricular and interventricular parts of the membranous septum. The attachment of the septal cusp of the tricuspid valve defines the division of the membranous septum *B* and *C* A membranous ventricular septal defect is shown in *B* with closure of the defect brought about by attachment of the septal leaflet of the tricuspid valve (*C*) The high pressure in the left ventricle can potentially cause bulging of the septal leaflet into the right atrium and simulate a membranous septal aneurysm. *D* A membranous septal aneurysm involving the atrioventricular portion and projecting into the right atrium. This situation would be difficult to distinguish angiographically from that shown in *C*. *E*, Membranous septal aneurysm of the interventricular portion projecting into the right ventricle. The aneurysm may extend and encroach on the septal leaflet of the tricuspid valve *a* or as is usually the case project toward the outflow tract of the right ventricle as in *b*.

septal aneurysm angiographically Massig[27] described a case in which part of the aneurysm sac was formed by the septal leaflet of the tricuspid valve Chesler Korns, and Edwards[28] recently described a similar pathological situation which may resemble an aneurysm of the membranous septum In their five cases there was an associated anomaly of the tricuspid valve. When a ventricular septal defect is closed by fibrous tissue[24] there is a potential weak spot present which may allow for the formation of an aneurysm It is interesting that one of the cases of Jain and Rosenthal[16] had a ventricular septal defect demonstrated by angiography after surgi

some other cardiac lesion is present a diagnostic evaluation will not be under taken. Therefore, in the majority of cases in which a clinical diagnosis was made an associated defect, usually a ventricular septal defect, was present. Baron and associates[6] have recently reviewed the diagnostic angiocardiographic features. The left ventricular angiogram usually revealed an outpouching from the left ventricular cavity below the aortic valve When the aneurysm was beneath the right coronary cusp t was usually best visualized in the lateral projection whereas when it is below the noncoronary cusp it is seen best in the frontal projection In all three cases of the present report the aneurysm was best visualized in the lateral position (Figs. 1 2 and 3) Visualization of the aneurysmal bulge should be noted before aortic opaci fication since a sinus of Valsalva aneurysm may dissect into the ventricular septum or bulge into a ventricular septal defect,[14,29] and present a similar radiographic picture. When the aneurysm is visualized before aortic opacification (Fig 1) the diagnosis of a septal aneurysm is more certain Supra aortic valvular angiography may be necessary if the diagnosis is uncertain since with this procedure only a sinus of Valsalva aneurysm will be visualized. However if aortic insufficiency is present the diagnosis may be difficult.

Summary

The pars membranacea separates the left ventricle from both the right ventricle and right atrium An aneurysm of this structure is uncommon. Three adult pa tients with a membranous septal aneurysm are presented in all 3 of them the aneurysm was associated with a ventricular septal defect. The etiology of these aneurysms is uncertain although there is evidence that they may be congenital defects related to malposition of the pars membranacea. There is also suggestive evidence that t may be due to an endocardial cushion defect, or result from a previously spon taneously closed ventricular septal defect. The majority of cases described in the l terature have been diagnosed at autopsy Though the lesion may occur as an isolated cardiac finding t is usually associated with congenital cardiac defects. The aneurysm may bulge into the right ventricle, the right atrium or directly against the septal leaflet of the tricuspid valve. It has rarely been reported presenting itself exterior to the heart. Occasionally the aneurysm may cause right ventricular outflow obstruction It may be complicated by endocarditis or by conduction and rhythm disturbance In order to make a clinical diagnosis, an angiocardiographic procedure is necessary

Addendum

Since completion of this article Yang and associates[16] reported two cases of membranous septum aneurysm. Both patients had small ventricular septal defects and both underwent surgical repair Harris and co-workers[17] in their series of patients with complete heart block reported another case in a 62 year-old woman[18,19] in which a membranous septum aneurysm had destroyed the bifurcation of the main bundle

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Table II Associated congenital cardiac defects

Defects	*Reference*
Coarctation of the aorta	24 26 37 42
Corrected transposition of the great vessels	15
Complete transposition of the great vessels	16
Dextroposition of the aorta	18
Right aortic arch	Case 1
Dilatation of the pulmonary artery	17 32
Hypoplasia of aorta	48
Aortic valve cusp deformity	17 20 30 50
Aneurysm of aortic valve leaflet	13 (as quoted by Lev and Saphir)
Sinus of Valsalva aneurysm	13 (as quoted by Lev and Saphir)
Aortic valvular stenosis	38
Subaortic stenosis fibrous	15 30, 37
Aortic insufficiency	37 43 50
Bicuspid pulmonary valve	17
Fenestrated pulmonary valve	51
Infundibular pulmonary stenosis	18
Mitral valve deformity	37
Ventricular septal defect, membranous type	6, 7 16, 24 25 32 34 39 41 44 45 47 48
Ventricular septal defect muscular type	44
Atrial septal defect, secundum	13 15 16 32, 39 50
Complete absence of atrial septum	52
Endocardial cushion defect	6
High origin of the coronary artery	13 17 30, 50
Persistent left superior vena cava	25
Anomalous right ventricular muscle bundle	30

the third case[44] because of a large mass within the cardiac shadow the patient was operated upon and the diagnosis made at surgery In this latter case the large size of the aneurysm caused the P wave vector of minus 30 degrees which was felt to be due to the posterior displacement of the right atrium

The aneurysms are usually 1 to 2 cm in diameter[38] the largest reported aneurysm measured 10 cm[40] They usually have a dome shape and a circular oval or triangular orifice measuring about 2 cm The orifice may have some evidence of calcification[38,46] It may occasionally have a multilocular appearance[17] The wall of the aneurysm has a fibrous structure with its cavity rarely being the site of thrombus formation[44] The aneurysm may occasionally be the site of bacterial endocarditis.[6,42,51,53] Rupture of the aneurysm with the production of a left ventricular–right atrial shunt may occur spontaneously[37,48] or as a result of bacterial endocarditis.[6] When associated with aortic insufficiency[38,16,43,49] it may occasionally be due to prolapse of the aortic valve leaflet.[34] Because of its proximity to the bundle of His it may be complicated by conduction and rhythm disturbances.[10,20,24,43,49] Its association with complete heart block[24,40] and varying degrees of atrioventricular block[19] have been reported

In most cases of ventricular septal aneurysm described in the literature the diagnosis has been made at autopsy With increasing utilization of angiocardiographic techniques the diagnosis has been made more frequently During the past ten years of 52 cases reviewed plus the present 3 cases the diagnosis has been made by angiocardiography in 31 patients, at surgery in 8 and at autopsy in only 16 cases. Since an isolated aneurysm will only occasionally be accompanied by a heart murmur[11,9,31,33,44] it is apparent that unless

some other cardiac lesion is present a diagnostic evaluation will not be undertaken. Therefore, in the majority of cases in which a clinical diagnosis was made an associated defect, usually a ventricular septal defect was present. Baron and associates[6] have recently reviewed the diagnostic angiocardiographic features. The left ventricular angiogram usually revealed an outpouching from the left ventricular cavity below the aortic valve When the aneurysm was beneath the right coronary cusp it was usually best visualized in the lateral projection, whereas when it is below the noncoronary cusp it is seen best in the frontal projection In all three cases of the present report the aneurysm was best visualized in the lateral position (Figs. 1 2 and 3) Visualization of the aneurysmal bulge should be noted before aortic opacification since a sinus of Valsalva aneurysm may dissect into the ventricular septum or bulge into a ventricular septal defect,[34,40] and present a similar radiographic picture. When the aneurysm is visualized before aortic opacification (Fig 1) the diagnosis of a septal aneurysm is more certain Supra-aortic valvular angiography may be necessary if the diagnosis is uncertain since with this procedure only a sinus of Valsalva aneurysm will be visualized However if aortic insufficiency is present the diagnosis may be difficult.

Summary

The pars membranacea separates the left ventricle from both the right ventricle and right atrium An aneurysm of this structure is uncommon Three adult patients with a membranous septal aneurysm are presented in all 3 of them the aneurysm was associated with a ventricular septal defect. The etiology of these aneurysms is uncertain although there is evidence that they may be congenital defects related to malposition of the pars membranacea. There is also suggestive evidence that it may be due to an endocardial cushion defect or result from a previously spontaneously closed ventricular septal defect. The majority of cases described in the literature have been diagnosed at autopsy Though the lesion may occur as an isolated cardiac finding it is usually associated with congenital cardiac defects. The aneurysm may bulge into the right ventricle the right atrium or directly against the septal leaflet of the tricuspid valve It has rarely been reported presenting itself exterior to the heart. Occasionally the aneurysm may cause right ventricular outflow obstruction It may be complicated by endocarditis or by conduction and rhythm disturbance In order to make a clinical diagnosis, an angiocardiographic procedure is necessary

Addendum

Since completion of this article Yang and associates[41] reported two cases of membranous septum aneurysm Both patients had small ventricular septal defects and both underwent surgical repair Harris and co-workers[9] in their series of patients with complete heart block reported another case in a 62 year-old woman[38,43] in which a membranous septum aneurysm had destroyed the bifurcation of the main bundle

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Fundamentals of clinical cardiology

Diuretic therapy—Current status

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In 1921 Vogl[1] and his associates accidently discovered the diuretic properties of a mercurial being used to treat syphilis. Since then the search for more powerful and orally effective agents has been continuous. The next phase in the development of the currently available diuretics also involved an antimicrobial agent. The observation that sulfonamides had the property of inhibiting the enzyme carbonic anhydrase eventually resulted in the mild diuretic acetazolamide.[2] In a further search for stronger carbonic anhydrase inhibitors the first truly potent oral diuretic, chlorothiazide, was produced in 1957.[3] However, it has only been within the last few years that oral drugs have been synthesized which are capable of producing a diuretic response greater than the effect of injected mercury. One of these, furosemide, is chemically related to the thiazides. The other is an entirely new type of drug, ethacrynic acid.

The importance of understanding the basic effect of these newer agents and the more familiar older drugs cannot be overstated. The most feared toxic effect of these recent additions is not a true side effect but is their ability to function continually under what would be adverse conditions for other diuretics. Thus, the degree of built-in protection against serious depletion afforded by the necessity of intermittent injections of mercury, which was to some degree compromised by the continuous use of thiazides, has been completely obliterated by the newer agents' ability to work continuously under a wide variety of circumstances.

Pharmacology

Edema is basically an imbalance between the intake of sodium and water and their excretion by the kidney. In the first analysis it is the retention of salt and secondarily water which leads to the edematous state, no matter what the initiating factors. Diuretics reduce edema in the simplest terms by increasing the excretion of sodium to a point where it exceeds the intake. In order to understand the action of these drugs it is first necessary to comprehend the normal renal handling of salt and water. The first step in urine excretion is the formation of an ultrafiltrate of plasma at the glomerulus. An increase in the production

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of this filtrate without concomitant increase in tubular reabsorption would result in a diuresis. None of the major diuretics increases delivery of sodium to the tubule by this method. Once filtered, the sodium is reabsorbed actively in the proximal tubule passively drawing water with it to produce an isotonic reabsorbate and isotonic tubular fluid. Under usual conditions up to 70 per cent of filtered sodium is reabsorbed in this area. As the fluid moves down the descending loop of Henle it becomes hypertonic due to the reabsorption of water and the addition of small amounts of sodium. In the ascending limb of the loop of Henle the tubule is impermeable to water and sodium alone is removed. Because of this unique property in the ascending limb, free water is generated here. Another site of free water generation or dilution ability occurs in the early distal tubule where a similar water impermeable segment exists.

The concept of free water and its opposite negative free water is important in determining the sites of action of diuretic drugs. Basically, they represent deviations of urine osmolality from plasma osmolality. Thus, when plasma and urine are isotonic with one another, the clearance of free water and negative free water is zero for both. In the well-hydrated state a dilute urine is excreted. Water is then being excreted in excess of solute. The measurement of this excess is free water clearance. It is calculated by subtracting the osmolar clearance from the total volume of urine excreted in cubic centimeters per minute. The clearance of osmoles is a measure of solute excretion. Free water clearance strictly speaking then is a quantitative measurement of the diluting ability of the kidney.

On the other hand, negative free water clearance is a measurement of the concentrating ability of the kidney in the dehydrated subject. It is the amount of water which would have to be added to concentrated urine to make it isotonic with plasma. The production of negative free water or concentrated urine depends on several factors. The first is the production of a hypertonic medullary and papillary interstitium. This occurs through the countercurrent multiplier mechanism which is present in the loop of Henle. The major functional component is again the water impermeable segment of the ascending limb of the loop of Henle. The sodium reabsorbed without water from the tubular fluid provides a major share of the interstitial osmotic forces which can raise the papillary tip osmolarity to over 1,200 milliosmoles per kilogram. Most of the remaining osmotic force is provided by reabsorbed urea. A second factor required for the production of concentrated urine is the ability of antidiuretic hormone to make the collecting ducts permeable to solute free water as the ducts pass through the hypertonic medulla.

Measuring the effects of diuretics on free water clearance and negative free water clearance can give much useful information about their sites of action. An increase in sodium reabsorption in the ascending limb of the loop of Henle results in an increase in free water clearance. Drugs which deliver increased amounts of sodium to this site lead to an increase sodium reabsorption in this area. Thus they can lead to increased generation of free water. To do this the action of the drug must be proximal to the ascending limb of the loop of Henle. Drugs which depress free water clearance can do so by preventing sodium reabsorption at either of the water impermeable sodium-reabsorbing sites. These are the ascending limb of the loop of Henle or the cortical diluting segment located in the early distal tubule.

However, if a drug depresses free water clearance as well as concentrating ability as measured by negative free water clearance, it can work only in the one area where both effects are generated, the ascending limb of the loop of Henle. It follows that a drug which only depresses free water clearance without effecting concentrating ability must have its primary site of action on the second water impermeable diluting segment located in the early distal tubule.

Further localization of drug effect can be demonstrated by the results of drug administration on potassium excretion. All the potassium filtered at the glomerulus is reabsorbed actively in the proximal tubule. Potassium excreted in the urine is the result of an exchange of sodium for potassium which occurs in the latter

portion of the distal tubule or the early collecting duct Here under the control of aldosterone and carbonic anhydrase sodium is reabsorbed and exchanged for potassium without a concomitant reabsorption of chloride. The amount of exchange occurring is determined to a great degree by the rate of delivery of sodium to this section of the tubule Thus a drug acting proximal to this site results in an increased sodium delivery to this area and increased sodium is made available for exchange with potassium The end result is not only an increase in sodium excretion but potassium excretion as well Drugs acting at this site result in increased sodium excretion of a mild degree with a concomitant decrease in potassium excretion

At the present time only two diuretics are known to exert a major portion of their effect in the proximal tubule Both of these mannitol and acetazolamide are presently used only infrequently in the treatment of edema However both have been extremely useful tools in studying renal physiology Mannitol is an alcohol derived from a hexose and is representative of the osmotic class of diuretics. Included therapeutically in this group are mannitol urea and isosorbide Glucose in large amounts has a similar mode of action in diabetics when the plasma level exceeds the tubular maximum All of these agents are effective when given intravenously only isosorbide and urea are active when given orally [4]

Following administration osmotically active agents produce tissue dehydration by obligating movement of tissue water into the plasma volume to equalize the increase in osmotic pressure [5] They are then filtered at the glomerulus and not reabsorbed As nonreabsorbable nonionic osmotic forces they prevent the reabsorption of water and reduce the active reabsorption of sodium by changing concentration gradients in the tubule.[6] A major portion of their effect is in the proximal tubule This results in an increased delivery of sodium to the ascending limb of the loop of Henle and allows the generation of increased amounts of free water [7]

Acetazolamide is one of the few diuretics in which the cellular action of the drug is well understood It is a blocker of carbonic anhydrase. This enzyme in the kidney is responsible for the generation of hydrogen ion which is then exchanged for sodium primarily in the proximal and distal tubule. Acetazolamide results in a mild increase in sodium and potassium excretion and a greater increase in bicarbonate loss. However even as a mild diuretic its usefulness is limited because the acidosis it induces results in refractoriness to its natriuretic effect [8, 9]

Two other diuretics would appear to have effects on proximal sodium reabsorption. Ethacrynic acid and furosemide both may act here however the volume depletion or decrease in glomerular filtration rate produced by these drugs leads to an increased proximal reabsorption of sodium cancelling this effect [9, 11] Their major site of action is known to reside in the water impermeable ascending limb of the loop of Henle These two drugs are relatively new extremely potent chemically unrelated diuretics that have essentially similar pharmacologic effects. They are rapidly active both intravenously and orally

Furosemide is a benzothiazide derivative however its mode of action is entirely different from that of the more familiar thiazides.[12] Initially the size of the natriuresis produced by this drug suggested that a proximal effect might be present however micropuncture studies failed to confirm these findings.[13] More recently several lines of evidence have suggested that a proximal effect does indeed exist. Bicarbonate excretion rises following the use of this drug to 10 to 15 per cent of the filtered load This finding suggests that a carbonic anhydrase-like activity may be present and that the loss of bicarbonate is due to proximal blockade of sodium reabsorption In addition phosphate excretion increases when furosemide is administered [14] Since phosphate reabsorption occurs only in the proximal tubule a proximal tubular effect of this drug can be deduced from these experiments. While it is generally agreed that furosemide usually decreases free water clearance, several investigators have noted that in some instances free water clearance rises.[13,15] This response suggests that at least under some conditions there is an increase in delivery of sodium to the ascending limb and therefore a proximal effect of this drug Finally

the same authors and others who initially reported failure to find micropuncture evidence of a proximal effect have recently pointed out certain technical problems in their original experiments. With a slightly different technique they have shown a significant proximal effect in micropuncture experiments.[10,11] However as stated before, while this is an interesting effect in terms of pharmacology it is doubtful that this effect contributes significantly to the resulting diuresis. The drug affects both the ability to concentrate and the ability to dilute urine as measured by a decrease in both free water clearance and negative free water clearance. [4] The only single area of the tubule which can be effected by a drug yielding such results is the water impermeable ascending limb of the loop of Henle. It is therefore assumed that the major mode of action is the inhibition of sodium reabsorption in this area. The resulting diuresis may be massive leading to a marked loss of sodium chloride bicarbonate and potassium

Ethacrynic acid is a derivative of phenoxyacetic acid and is capable of producing a massive diuresis of up to 45 per cent of the filtered load of sodium.[18] It has now been shown also to have a mild proximal effect by micropuncture studies, and like furosemide, it causes both a decrease in free water clearance and negative free water clearance.[12, 1-21] Therefore it works primarily in the ascending limb of the loop of Henle.

While the above evidence is generally accepted as indicative of action in the ascending limb of the loop of Henle, there is some data which is inconsistent with these results. Nechay[22] testing the effects of ethacrynic acid in the chicken noted that the effect in this species is equivalent to that in other animals. This occurs despite the fact that anatomically the chicken has a very poorly developed loop of Henle, which raises some question as to whether it should work in this species at all. So far this inconsistency has not been explained. Barger and his co-workers[23] using krypton and other radioisotopic methods, have studied blood flow in animals undergoing diuresis with both furosemide and ethacrynic acid. These studies reveal a shift in blood flow from medullary to cortical areas. Whether the primary effect of these drugs is due to vascular changes rather than a cellular action within the tubule is unknown. It is entirely possible that the blood flow changes may be secondary to the diuresis. There is, however agreement that no matter how it occurs, the medullary interstitial gradient built by the countercurrent mechanism is effectively dissipated by both of these drugs.[24,25]

Ethacrynic acid and furosemide work at lowered filtration rates, in the presence of hyponatremia azotemia hypochloremia acidosis, and alkalosis.[22] While the two drugs are essentially similar in action and apparent effect, there are several differences between them. Ethacrynic acid does not increase bicarbonate excretion to any degree. In addition the excretion of titratable acidity and ammonia rise with its use.[27] The result is a primary loss of sodium chloride, and to a lesser degree potassium. As sodium and chloride are lost plasma volume falls and bicarbonate rises resulting in an alkalosis.[19] Another difference is that furosemide has a steep dose response curve which is not shared by ethacrynic acid.[26]

A large group of drugs, the thiazides, have their major site of action further along the tubule in the proximal portion of the distal tubule. There are multiple drugs of this type available today. Basically they all share the same site of action and effect. Chlorthalidone which has a different basic chemical structure, has a similar effect and site of action. The site of action is again basically localized by the drugs effect on free water clearance and negative free water clearance. They have no effect on concentrating ability but they do decrease free water clearance. Thus, instead of affecting the ascending limb of the loop of Henle where both these parameters are localized they must have their major locus of action in the second site of free water generation. This is in the cortex, in the proximal segment of the distal tubule, where the tubule is again impermeable to water and sodium can be reabsorbed without water. A blockade of sodium reabsorption at this site results in the presentation of increased amounts of sodium to the distal part of the distal tubule. This leads to an increased potassium for sodium exchange and increased potassium excre

tion While the inhibition of carbonic anhydrase could account for some of this potassium loss it is known that the very mild carbonic anhydrase inhibitory activity present in most of these drugs is not sufficient to explain the kaluresis [23]

A great deal of time effort and space has been spent both in journals and advertising to suggest that one or the other of the multitude of available thiazide drugs is the preferred agent because of a specific decrease of potassium excretion compared to sodium loss. The problem is probably a far more basic nonspecific effect of these drugs and almost all other diuretics. The more effective the agent the more sodium will be delivered to the distal sodium potassium exchange segment Since the activity of this segment depends to a great degree on the amount of sodium presented to it more potassium will then be exchanged for sodium and potassium excretion will rise Moreover the volume contraction associated with a successful diuresis will increase aldosterone secretion Secondary aldosteronism then further stimulates the distal sodium potassium exchange mechanism further increasing the exchange of potassium for sodium [24] Therefore the more effective the drug the more effective the diuresis which then results secondarily in more potassium loss. In fact there is no clinically significant difference among the thiazides in the ratio of sodium to potassium excreted

While there is a great deal of physiologic data available about mercurials the exact site of action escapes detection or at least agreement The mercurials are extremely effective diuretics resulting in an excretion of up to 20 per cent of the filtered load of sodium or about two times the maximum effect of thiazides [25] They result in an almost equal loss of chloride and sodium leading to a systemic hypochloremic alkalosis When this happens mercurial diuretics lose their effect. This can be restored by elevating the serum chloride or increasing the chloride in the urine through the use of ammonium chloride arginine hydrochloride or lysine hydrochloride [24, 26] Production of a nonspecific acidosis by sodium nitrate also restores their action However a respiratory induced acidosis appears to have no effect on the production of the diuresis. Levitt and Goldstein[20] have suggested that the means of producing the acidosis is of prime importance According to them most methods of inducing systemic acidosis lead to an increased sodium delivery to the distal tubule through the filtration of an impermeant anion. Their final conclusion is that any technique which increases sodium presented to the distal tubule and in which the urine is acid will result in an enhanced diuresis following mercurial administration

Studies with mercurials in the past have suggested that free water clearance increases following their administration [40] This led to a belief that a proximal site of action was involved All but one of the commercially available mercurials has as a carrier molecule theophylline or a theophylline derivative Theophylline causes an increase in free water clearance when given alone Mercurials without theophylline cause no change in free water clearance or negative free water clearance. It can be suggested from this data that mercurials do not act in the proximal tubule the ascending limb or the cortical area responsible for free water generation.[41, 42] Therefore they must work in the distal tubule beyond the cortical diluting segment

It has been known for a long time that mercurials depress sodium for potassium exchange in the distal tubule if potassium excretion is initially high [43, 44] While this decrease in potassium excretion may be a factor in preventing hypokalemia from occurring with the use of mercurials, intermittent administration may be a far more important feature A massive diuresis may produce a large potassium loss and hypokalemia [23] This plus the fact that chloride excretion exceeds sodium excretion does suggest that some potassium for sodium exchange is preserved in the distal part of the distal tubule. Action at the distal sodium potassium exchange site alone could not produce the resulting diuresis therefore it seems best to assume that the most likely site of maximal action lies in the distal tubule between the distal cortical diluting segment and the distal sodium potassium exchange area probably including part of the latter

Despite this data the most recent re-

views on the mercurial diuretics suggest that mercury probably has an effect *throughout the entire nephron*[38] It is true that a balanced effect on both proximal and distal nephron areas could result in the lack of changes in free water clearance and negative free water clearance noted in the above mentioned studies. It is unlikely that this would occur In addition early micropuncture studies reported by Clebusch[43] suggest a proximal effect, but Dirks and associates,[12] in their most recent experiments, *fail to confirm these results.* Other data presented in these reviews indirectly support a proximal effect. It is most disconcerting to realize that despite its long clinical use there is still a great deal to be learned concerning the basic effect of the mercurial diuretics on the nephron

The final two diuretics in common use act at the most distal part of the distal segment and in the early collecting duct at the sodium-for-potassium exchange site. Both Aldactone and triamterene are mild diuretics and useful mostly as adjunctive drugs.[44,47] They result in a decrease of potassium in the urine and an increase of sodium and chloride excretion in equal amounts. Aldactone works by blocking the action of aldosterone on the tubule.[48] It takes several days for the effect to become apparent and the presence of normally active adrenal glands is required for the drug to be effective Triamterene results in a similar diuretic effect however while it superficially appears to be an antialdosterone agent it works well in the absence of adrenal glands, indicating a basic tubular action.[49] It also works shortly after being administered

The above conclusions concerning the mode of action of the useful diuretics is a synopsis of the *currently available literature.* Much of the conflicting data has been purposely ignored to present a concise current concept The area is one of rapid change and in view of current advances subject to frequent re-evaluation.

Clinical application

The pharmacologic principles already presented must be combined with a full understanding of the patient's pathophysiologic state in order to make rational use of the available diuretics. The first symptoms of congestive heart failure respond dramatically to salt restriction bed rest, or digitalis. They also may respond to small doses of a wide variety of diuretics. Consequently vigorous treatment with potent diuretics, especially coupled with severe sodium restriction is unnecessary and will only lead to problems. With increasing severity of symptoms the need *for more effective diuretics is obvious.* It is then reasonable to anticipate the problems which are known to be associated with these agents. Some of these problems are present with only one category of diuretic while others are related to the use of all diuretics. These general problems may involve excessive therapeutic effect, potassium changes, aggravation of hepatic disease the elevation of blood urea and hypersensitivity reactions.

Removal of salt and water is the desired effect of diuretic therapy however serum *sodium is not a measurement of total body* sodium and therefore serum sodium levels cannot be used as a guideline to the adequacy of diuretic therapy Despite hyponatremia there is an increased total body sodium if edema is present. Dilutional hyponatremia is not a direct consequence of diuretic therapy but can be aggravated by inappropriate administration of water or diuretics. Dilutional hyponatremia results from an inability of the kidney to excrete a water load an inability which is common in all of the edematous states. Moreover *inappropriate thirst is frequently a consequence* of salt restriction and diuretic therapy Thus, free access to water during this period linked with the defect in water excretion is the usual cause of dilutional hyponatremia. Sodium depletion is impossible if edema is present and consequently sodium administration will only aggravate the underlying condition. The falsely lowered serum sodium found in the *hyperlipidemic and hyperproteinemic* states does not indicate sodium depletion since plasma water sodium is normal.[50]

True sodium depletion may occur but is extremely unusual. In order to make a diagnosis of chronic sodium depletion edema must be absent. Serum sodium may be low or normal. Lethargy somnolence and especially postural hypotension are frequent symptoms of true sodium deple

tion Muscle cramps and weakness may be present. Sodium depletion can result from the overuse of very effective diuretics and simulates the findings in chronic salt wasting renal disease It is in this rare circumstance that discontinuation of the diuretic and sodium repletion is necessary

All of the diuretics except the spironolactones and triamterene may cause a potassium loss as well as a natruresis. With an increased delivery of sodium to the potassium-secretary site in the distal nephron coupled with the secondary hyperaldosteronism associated with the edematous state the system is set for a marked kaluresis Profound weakness even paralysis and the changes of the kaliopenic nephropathy and myopathy occur as a direct effect of chronic potassium depletion [81] Increased sensitivity to digitalis preparations and an inability to repair an alkalosis are side effects. The potassium problems with diuretics are well recognized by most physicians, but the magnitude of the deficits are little appreciated and cannot be readily ascertained by clinically available tests. The serum potassium is a notoriously poor reflection of the total body potassium The development of an alkalosis results in a lowering of serum potassium while an acidosis elevates serum potassium Neither of these changes indicates a change in total body potassium In the presence of a deficiency potassium administration without concomitant chloride administration will not replete the potassium however if adequate chloride is present in the diet, other potassium salts may be used to prevent depletion [illegible] It is generally not appreciated that patients may respond to a diuretic with kaluresis without natruresis. This is most likely to occur in patients in whom the glomerular filtration rate is reduced and the effective plasma volume decreased with resulting hyperaldosteronism and a low urine flow rate. Thus when an increased sodium load is presented to the distal tubular sodium potassium exchange mechanism it is not enough to overwhelm this exchange Consequently this sodium load is almost completely reabsorbed and potassium excreted instead

The potassium depletion and alkalosis resulting from many forms of diuretic therapy may aggravate hepatic coma however there is no indication that diuretic usage causes the hepatorenal syndrome [illegible] Elevation of blood urea may result from use of virtually any diuretic Two factors are causally important in this urea elevation The first is a decrease in glomerular filtration rate resulting from a decrease in effective plasma volume. The lowered glomerular filtration rate results in an elevation of both blood urea nitrogen and plasma creatinine. The second cause is an increased reabsorption of filtered urea. Here plasma creatinine is normal or near normal and blood urea nitrogen is elevated out of proportion to the creatinine level.

Idiosyncratic reactions have been reported with every diuretic Hypersensitivity manifested as a skin reaction is the most common example Generalized maculopapular eruptions petechial eruptions, erythema multiforme vesicular erythema with photosensitivity lichen planus, and urticaria have all been encountered.[37]

The problems already mentioned are associated with all diuretics. Each class of diuretics has, in addition specific uses and problems

The osmotically active diuretics have a very specialized place in clinical usage. Urea mannitol and isosorbide are the most commonly used They are effective very rapidly Consequently they are useful in initiating a diuresis abruptly such as when there is brain edema during aortic surgery or in testing acute oliguric renal failure [illegible] The initiation of a diuresis after drug ingestion can readily be accomplished with one of these osmotically active agents.

Any osmotic diuresis, either natural or administered prevents the conservation of sodium and water If adequate water is not provided and lost with the osmotic diuresis, hypernatremia will develop [illegible] If adequate water and inadequate sodium is administered hyponatremia will develop. Hyperosmolality and intracellular dehydration rapidly occur if a large amount of solute diuretic is given and not excreted [illegible] Acute expansion of the extracellular fluid volume can also lead to pulmonary edema The utilization of one half normal saline solution to replace the losses from a mannitol diuresis will prevent any significant electrolyte imbalance if the diuresis is not continued for an excessive time period [illegible]

Spironolactone in high doses adminis-

tered for a prolonged period will control all the abnormalities of primary aldosteronism.[66,44] Other than this specialized use, both spironolactone and triamterene are only useful as adjuncts to other diuretics. By themselves, they are very weak diuretics and only can cause a specific natruresis if sufficient sodium is delivered to the distal tubular sodium potassium exchange site. Blockage of the exchange at this site will allow more sodium and less potassium to escape into the urine. This potassium-sparing effect may be of benefit to some patients taking digitalis. Since the edema associated with cirrhosis and the nephrotic syndrome is so greatly influenced by secondary hyperaldosteronism the decrease in the aldosterone effect caused by the use of these drugs may be especially useful. All of the potassium excreted in the urine normally is by exchange and consequently a blockage of this exchange may result in marked hyperkalemia. This is most prominent when one of these agents is given in combination with potassium or when both spironolactone and triamterene are given concomitantly.[67,44]

The mercurial diuretics still command a great deal of attention because of their extreme usefulness. All of these diuretics available for parenteral use contain 39 mg Hg per cubic centimeter except mercaptomerin which has 40 mg per cubic centimeter. The maximum effect of these drugs is attained with 80 mg Hg, and consequently there is little need to exceed 2 ml per dose. Fifty per cent of the mercurial is excreted in three hours and 75 to 95 per cent within 24 hours. It is probable then that administration every 24 hours will result in an accumulation within the body even in the patient with reasonably normal renal function. Less frequent doses are therefore mandatory.[69]

The onset of action of any mercurial is within 1 to 2 hours with a peak action of between 6 and 9 hours and a duration between 12 hours and 24 hours. Intravenous use is rarely if ever justified since the intramuscular absorption is so rapid and the hazard of ventricular fibrillation with intravenous use is prominent.[70] It is better to use furosemide or ethacrynic acid when intravenous therapy is necessary. Mercurial absorption from an edematous area is unpredictable and such administration should be avoided.

Mercurials, as have been mentioned, are ineffective if there is alkalosis or hypochloremia. In effect these act as built in safety valves against the further progression of alkalosis. Since they do not produce the degree of kaluresis seen with the thiazides, furosemide or ethacrynic acid mercurial diuretics are especially valuable in the patient prone to potassium depletion.

If the serum chloride level is below 102 mEq per liter it should be increased by the administration of 100 to 175 mEq a day of chloride as ammonium chloride, lysine hydrochloride,[72] or arginine hydrochloride,[7] for 2 to 4 days prior to the injection of the mercurial. Since ammonium chloride tablets are enteric-coated they are frequently not absorbed. The use of ammonium chloride solution is preferred. In patients with liver failure ammonia metabolism is abnormal and ammonium chloride administration should be avoided.

A satisfactory diuresis is dependent on an adequate renal plasma flow. This is especially so with the mercurials. Aminophylline which increases renal plasma flow when administered 1 to 2 hours after a dose of a mercurial will greatly increase the diuresis. An avoidance of the decreased renal plasma flow normally associated with the upright position is also beneficial. The nonspecific vasodilatation effect of isoproterenol may be helpful in increasing the renal plasma flow in a patient who does not have coronary artery disease.[49]

The mercurials have been reported to have caused the nephrotic syndrome and membranous glomerulonephritis, and to have permanently aggravated chronic renal failure.[72,73] It is therefore prudent to determine the patients renal functional status and electrolyte composition before giving a mercurial diuretic. This is especially true if one dose produces little or no effect and a second is contemplated.

Since the benzothiadiazine derivatives and chlorthalidone are rapidly and completely absorbed from the gastrointestinal tract, they have become the mainstays of chronic diuretic therapy. The continuous administration of thiazide diuretic leads to hypokalemic alkalosis, the most important unwanted side effect. Kaluresis without natruresis is more frequent with

the thiazides th in with any of the other diuretics. Intermittent administration of the diuretic is to be encouraged if possible since it will allow potassium conservation during the interval between doses and will obviate the need for supplemental potassium Hyperuricemia is a metabolic complication of the use of the thiazide di uretics.[74, 77] The reason for the hyper uricemia is still not fully explained Extra cellular fluid volume contraction or an alteration in the renal reabsorption of urate are the two mechanisms most frequently proposed The nondiuretic thiazide diaz oxide also causes hyperuricemia despite its tendency to expand rather than con tract the extracellular fluid volume[78] Despite hyperuricemia clinical gout rarely occurs except in previously gouty pa tients.[79]

Mild hyperglycemia most prominent in diabetic patients and in those with a genetic history suggesting diabetes mellitus is quite common The hyperglycemic effect is not marked and although requiring an alteration in the therapy of a diabetic pa tient rarely is it a significant problem[80, 81]

Because of the effect on free water clear ance there is a prominent tendency toward dilutional hyponatremia with the chronic administration of a thiazide Pan creatitis a generalized vasculitis and hepa tocellular jaundice as well as thrombocytopenia neutropenia have been reported with the thiazide diuretics but are rare and must be considered as idiosyncratic reactions.[84, 86] Thiazide diuretics are fre quently part of a weight reduction program but this use is to be deplored The weight loss produced by the diuretic involves no loss of fat or lean body mass and may only add to the metabolic aberrations caused by any severe dietary restriction

Ethacrynic acid and furosemide are two extremely efficacious diuretics which have been released for clinical use in the past few years. These drugs can be administered orally and intravenously while furosemide also can be given by intramuscular injection These agents have replaced the mercurials for intravenous use in crisis situations having an onset of action within minutes with the maximum diuresis being achieved in 4 hours[81] If administered by mouth their effect again is very rapid with a peak within 2 hours.

Ethacrynic acid has been noted to decrease cardiac output pulmonary vascular volume and plasma volume rather abruptly[82, 83] Excretion in excess of 32 per cent of filtered sodium 47 per cent of filtered chloride and 46 per cent of filtered water during the maximum diuresis has been reported Similar excretions occur also with furosemide[14] Such a massive diuresis can obviously lead to the very rapid development of severe fluid and electrolyte problems. Two of these problems contraction alkalosis and potassium depletion warrant separate comment.

Both ethacrynic acid and furosemide cause a marked chloruresis.[81] The chloride excretion approximates the sum of sodium and potassium excretion Following ethacrynic acid administration very little excretion of bicarbonate occurs. In fact despite the development of a systemic alkalosis renal hydrogen ion excretion may continue. With furosemide there is some excretion of bicarbonate but the amount is frequently insignificant when compared to the chloride loss. The hypochloremic alkalosis that develops is due to shrinkage of the extracellular fluid compartment with little change in total body bicarbonate. This causes a rise in plasma bicarbonate concentration[89] Moreover unlike the mercurial diuretics both of these agents remain effective despite hypochloremia or alkalosis.

Despite early reports to the contrary both drugs cause significant kaluresis.[82, 83] As could be anticipated this is most marked in those conditions associated with hyperaldosteronism The potassium depletion tends to be compounded by the problem of alkalosis and potassium repletion cannot be accomplished without chloride repletion[86, 87] Furthermore there is a rather marked individual variability in response to a given dose of either di uretic. Ethacrynic acid has a narrow range between minimum and maximum effective dosage while furosemide has a very wide range Choice of dosage to be administered is consequently a problem

Davidov and associates[88] has published a table of starting and maintenance dosages for parenteral furosemide therapy in patients who have normal renal function They advise beginning with 40 mg in the patient who has had diuresis

od 80 mg in the patient no longer responding well to other diuretics. They then suggest using the response in the next 2 hours as a guideline for further therapy if the response has been satisfactory the starting dose is given twice a day but if the response has been unsatisfactory the dose is doubled and then administered twice a day

The therapeutic effectiveness of each of these diuretics under a variety of conditions leads to some special uses. The ability to produce a marked chloruresis has been utilized in the treatment of bromism since bromide excretion is also increased.[**] The prompt diuresis has led to claims of effectiveness in the control of pulmonary edema, but Leach and associates[**] found no correlation between the rapidity of diuresis and the clearing of pulmonary edema. Both drugs are also effective despite renal failure.[17,1**] Patients with mannitol-resistant, oliguric acute renal failure have responded to either ethacrynic acid or furosemide when given in high dose.[**,1**] Maher and Schreiner[**] have noted urine volumes as high as 15 per cent of the estimated glomerular filtration rate after ethacrynic acid administration to uremic patients. They reported using doses as high as 8 mg. per kilogram of body weight per day.[**] Muth[**] has reported beneficial results with the use of furosemide in patients with renal failure. He has given up to 2 Gm. of furosemide in one dose and up to 4 Gm. per 24 hours. He suggests beginning with 320 mg. per day by mouth in the patient with a creatinine clearance below 30 milliliters per minute. In emergency situations, when the blood urea nitrogen is greater than 30 mg. per cent, he advises an initial parenteral dose of 100 mg. doubled every 1 to 2 hours until there is an effect. In order to maintain a steady diuresis he also suggests that administering two thirds of the oral dose in the morning and one third in the afternoon is more efficacious than giving the medication either in a single dose or evenly divided doses.

Beside the fluid and electrolyte problems mentioned, several other problems are also attributable to ethacrynic acid and furosemide. They both share with the thiazides the problem of hyperuricemia and rare cholestatic jaundice.[1**-1**] Hyperglycemia has been associated with furosemide therapy but not with ethacrynic acid.[1**-1**] Diarrhea and gastrointestinal distress have been reported with the use of ethacrynic acid.[**] Profound hypoglycemia with convulsions has occurred in several uremic patients 2 to 3 weeks after high doses of ethacrynic acid were administered.[**] In uremic patients, deafness has also been reported. This has usually been abrupt and transient although occasionally permanent.[**] The chief current problem with the use of both of these diuretics is the failure to understand that they may produce an excessive diuresis.

Conclusion

When there was only one effective class of diuretics, the physician had only the choice of using or not using the diuretic. The present availability of a number of potent diuretics now offers a wide choice of agents of varying pharmacology. The clinician must not only decide whether to use diuretics or not, but must also integrate the various drugs' pharmacology with the patient's pathophysiology and decide upon drug and dosage. It is not enough to know that a certain drug will work. The magnitude of the response to a given dose, the rapidity of onset, plus the water and electrolyte alterations that will ensue must be anticipated. Potential side effects and idiosyncratic reactions must be weighed carefully before choosing a drug and the dose of that drug. The pharmacology which has been outlined is only a nucleus of information to which must be added the patient's pathophysiology in order to achieve rational therapy. The favorable clinical experience with mercurial and thiazide diuretics gained with long usage has made them the preferred drug for routine use. The other diuretics offer variations which are helpful in the complicated and resistant patient.

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Appraisal and reappraisal of cardiac therapy

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The treatment of endocarditis

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The clinical and bacteriologic spectrum of endocarditis is undergoing constant evolution. Advances in cardiac surgery the availability of effective newer antibiotics, the widespread use of immunosuppressive agents, and changes in the epidemiology of bacterial infections necessitate periodic review of current practice in the treatment of endocarditis. In the years before antibiotics, endocarditis was universally fatal In this disease, as in no other the knowledgeable use of antibiotics, under appropriate laboratory control is a lifesaving procedure.

Although some authors have reported favorable experience with the treatment of endocarditis for as brief a period as two weeks, this therapeutic compromise is to be avoided in a disease of this gravity To offer the patient the best chance of a bacteriologic cure, prolonged administration of high doses of an effective antibiotic is essential. Three to four weeks can be considered adequate only in uncomplicated cases of endocarditis due to highly sensitive strains of viridans streptococci which are killed in vitro by 1 μg per milliliter or less of penicillin G Four to six weeks is mandatory in infections due to other organisms, with the longer period preferable in all postoperative infections and those caused by more resistant organisms.

The choice of an antibiotic should be governed both by the nature of the infecting organism and by quantitative tube-dilution antibiotic sensitivity tests to determine bactericidal concentration. Bacteriostatic drugs (chloramphenicol, the tetracyclines, and generally lincomycin and erythromycin) should be avoided Although they may suppress all clinical and laboratory manifestations of active disease and even restore a feeling of well being to the patient, the relapse rate is exceedingly high even after prolonged treatment. Disc sensitivities, as routinely performed in clinical bacteriology laboratories, are an inadequate guide to therapy since they do not distinguish bactericidal from bacteriostatic activity and for penicillin G do not separate more sensitive (killed by less than 1 μg per milliliter) from relatively resistant (not killed by 1 μg per milliliter) streptococci. This differentiation is of considerable therapeutic significance.

During therapy it is desirable to monitor antibiotic treatment with determinations of the bactericidal activity of the patient's serum against the infecting organism. Just as quantitative antibiotic sensitivities offer the most appropriate guide to selection of an antibiotic the antibacterial activity of the serum is the best indication of the adequacy of treatment. Since the organisms in endocarditis lie deep within fibrin vegetations, they are effectively insulated from the host's humoral and cellular defenses

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and the antibiotic alone must effect a cure. The serum test itself is a simple serial dilution and should be within the technical capabilities of all hospital bacteriology laboratories.[1] In general if the patient's serum is bactericidal i e kills an inoculum of infecting organisms in a dilution of 1:8 or greater the physician may be reasonably certain of the adequacy of therapy Failure of the serum to achieve this activity is an indication for upward adjustment of dosage or change of treatment to a more effectively bactericidal antibiotic

Streptococci of various groups account for the vast majority of bacteriologically proven cases of endocarditis Penicillin G alone is the ideal treatment for those strains of viridans streptococci for which it is bactericidal in a concentration of 1 μg per milliliter or less. Clinical results in this group are almost uniformly excellent. Whenever the infecting organism is an enterococcus (Group D) or is a relatively resistant viridans streptococcus (bactericidal concentration greater than 1 μg per milliliter) penicillin alone cannot be relied upon to eradicate the infection and an aminoglycoside antibiotic such as streptomycin must be given concomitantly In some cases of enterococcal endocarditis particularly when relapse occurs following a supposedly adequate course of treatment, ampicillin in doses of 12 to 30 Gm per day plus streptomycin or kanamycin may offer an advantage over penicillin G and streptomycin Both viridans streptococci and enterococci usually cause the syndrome of subacute bacterial endocarditis but enterococci may occasionally present as acute bacterial endocarditis with septic fever widespread embolization and rapidly progressive course Group A beta hemolytic streptococci as well as microaerophilic and anaerobic streptococci occasionally cause endocarditis These organisms are almost uniformly killed by less than 1 μg per milliliter of penicillin G and are usually treated with penicillin G alone

After streptococci of all types, staphylococci both coagulase positive and negative are the most common cause of endocarditis and they are the most frequent pathogens in postcardiotomy endocarditis Staphylococcal endocarditis involving the right side of the heart is often seen in heroin addicts. Although most staphylococci are resistant to penicillin G by virtue of their elaboration of penicillinase recent reports have indicated that penicillin-sensitive staphylococci have been isolated with increasing frequency during the past decade even within the hospital setting Here again quantitative tube-dilution antibiotic sensitivity tests are vital to distinguish penicillinase-producing from non-penicillinase producing staphylococci In general staphylococci which are killed by 1 μg per milliliter or less of penicillin G are not capable of producing penicillinase, and should be treated with massive doses of penicillin G Penicillin resistant staphylococci are almost always sensitive to one of the semisynthetic penicillinase-resistant penicillins and should be treated with oxacillin or nafcillin in doses of 12 to 24 Gm per day by intermittent intravenous injection In recent years, staphylococci resistant to all semisynthetic penicillins and cephalosporins have appeared in the United States. To eradicate these organisms it is usually necessary to resort to treatment with a more toxic antibiotic such as vancomycin or kanamycin.

The gram negative bacilli and a wide variety of less common pathogens, such as diphtheroids, *Streptobacillus moniliformis* and members of the Hemophilus group, may also cause endocarditis. In these infections as well therapy must be guided by quantitative bactericidal antibiotic sensitivity tests and serum antibacterial activity Fungus endocarditis presents a particularly difficult therapeutic problem since chemotherapy with amphotericin B the only effective systemic antifungal antibiotic is only occasionally successful and most cases terminate fatally

Blood cultures are negative in 10 to 15 per cent of cases of endocarditis. The absence of laboratory guidance to the selection of an effective antibiotic and the inability to monitor therapy with serum bactericidal activity are reflected in the somewhat higher mortality rate of abacteremic cases. The clinical syndrome of subacute endocarditis in a patient with rheumatic or congenital heart disease is best treated as enterococcal infection since the enterococcus is the most difficult to eradicate of the common pathogens in

this setting. If the patient has undergone cardiac surgery, the problem of antibiotic selection is magnified by the wide variety of bacteria and fungi which may be involved. In abacteremic postoperative cases it is probably best to initiate treatment for staphylococcal endocarditis, with early reoperation planned if the clinical response is not prompt. It is interesting to note that aspergillus endocarditis characteristically has negative blood cultures and frequently presents as large vessel emboli from which the organism may be recovered.

The penicillin allergic patient presents a special therapeutic challenge. Unless there is a clear history of immediate anaphylactic reaction to penicillin in the past, it is probably safe to administer penicillin with appropriate safeguards at the initiation of therapy. Those patients with an anaphylactic history can frequently be desensitized, following which penicillin can be given in usual therapeutic doses. Should desensitization prove impossible, cephalothin can often be substituted with safety, avoiding the more toxic alternative of vancomycin. The appearance of a drug rash during treatment rarely necessitates a change in therapy since the eruption will usually subside with antihistamine treatment despite continued administration of penicillin.

Although most cases of endocarditis are optimally treated with antibiotics alone, three clinical situations may warrant surgical intervention during the early stages of the disease. Acute valve perforation, most commonly involving the aortic valve, may result in sudden severe and intractable congestive failure, and emergency valve replacement may be lifesaving. Surgical intervention may also be necessary to remove the large vegetations which occur in candida and other fungus infections of the heart, particularly if large vessel emboli or valvular obstruction present serious problems. Additionally, in postcardiotomy endocarditis, reoperation to remove infected foreign material may be necessary early in the disease when the patient does not respond promptly to medical therapy alone, or when there is definite evidence of prosthetic valve malfunction.

Endocarditis is unfortunately a frequent complication of cardiac surgery, particularly when the pump oxygenator is used. Several series report an incidence as high as 5 to 10 per cent. In all likelihood the infecting organisms are introduced at the time of surgery, and particularly in valve replacement, the foreign body acts as a nidus of infection. Despite a lack of evidence supporting the value of "prophylactic" antibiotics, nearly all surgeons prescribe antibiotics during the immediate postoperative period and frequently preoperatively as well. Usually penicillin G and/or a penicillinase-resistant penicillin are given, and in most cases, streptomycin or another drug with activity against gram-negative organisms is added. Because prophylactic antibiotics suppress the patient's sensitive normal bacterial flora, postcardiotomy endocarditis is frequently caused by resistant organisms which have rarely been associated with endocarditis in the past. Methicillin and oxacillin resistant strains of *Staphylococcus aureus* and *albus*, multiply resistant gram negative enteric bacilli, *Candida albicans*, and a wide variety of more unusual bacteria and fungi may be found. The diagnosis must be strongly suspected whenever the patient develops fever during the weeks following surgery, and is confirmed by the presence of positive blood cultures. Ancillary clinical signs of endocarditis, such as petechiae and splenomegaly, are frequently absent.

In every case of postoperative endocarditis, reoperation for removal of infected sutures or prosthetic valves must be considered. Unquestionably the presence of any foreign body makes the infection more difficult to eradicate, and increases the likelihood of relapse. Resistant infections, in which adequate bactericidal serum activity cannot be achieved, generally require reoperation, even if the clinical response appears satisfactory. Similarly very few cases of fungus infection can be successfully treated medically. Because of the large size of fungus vegetations, it is virtually impossible to sterilize these lesions with amphotericin. The vegetations are particularly friable, frequently cause large vessel emboli, and may be of sufficient size to be hemodynamically significant.

A high proportion of cases of post-cardiotomy endocarditis, however, are caused by organisms such as enterococci and most

staphylococci which are amenable to medical therapy alone. Many strains of *Staphylococcus albus* which are resistant to oxacillin methicillin and nafcillin remain sensitive to cephalothin and can be successfully treated with this agent. If the patient improves clinically with effective antibiotic treatment confirmed by adequate serum bactericidal levels and there is no evidence of valve malfunction surgery is rarely necessary unless relapse occurs after six weeks of treatment.

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Annotations

Analgesics in myocardial infarction

The lungs have not only to ensure that blood and gas mix with each other but that they do so efficiently. If blood flow to an area of lung to which the supply of oxygen is less than that required to maintain adequate saturation, then cardiac effort is wasted and, more importantly, blood returns with its oxygen storage capacity underutilized. At normal atmospheric pressures and with an unimpaired ventilation, the oxygen-carrying capacity of hemoglobin is virtually fully utilized and the oxygen carried in physical solution is minimal (19 ml. of oxygen combined with hemoglobin but only 0.3 ml. in solution). Therefore, although air supply to another area may bring oxygen in excess quantities to the blood, this cannot compensate for relative overperfusion. The mixed blood returning to the left atrium from these two areas will be less than fully saturated. The superfluous cardiac output is frequently referred to in terms of the size of a right to left shunt having an equivalent effect on arterial blood saturation. Because of the slope of the oxygen dissociation curve, a more sensitive way of localizing it (than in terms of mere saturation) is the difference in oxygen tension (pO_2) between gas in the alveoli and in arterial blood (A-a O_2 gradient).

There may also be superfluous ventilation due to underperfusion and this is frequently referred to in terms of the size of an additional (physiologic) dead space to total ventilation (V_D/V_T).

In the erect posture the weight of the column of blood causes a relatively greater blood flow to the dependent parts of the lung per unit of ventilation than to the upper lobes. There is good reason to suppose that with normal pulmonary artery pressures virtually no blood flows in the apices in the erect posture, implying an uneven distribution in ventilation and perfusion throughout the lung, and it is consequently reflected by an increase in the V_D/V_T ratio and the A-a gradient.[1] This uneven distribution exists even in the supine posture although it is of less magnitude because the blood column measured from the front to the back of the chest is less than that measured from apex to base.

The V_D/V_T ratio and A-a gradient have been shown to be increased in myocardial infarction by Pain and associates[2] and McNicol and co-workers.[3] Left ventricular failure or lowered pulmonary artery pressure and reduced pulmonary blood flow have been proposed as the cause of this. Moreover Lal, Savidge, and Chhabra[4] showed that V_D/V_T ratio and A-a gradients were significantly higher among those patients with cardiac infarction in the acute phase who subsequently died than among those who recovered. The effect of hypotension in this [illegible] sore. Drugs like pethidine, morphine, and heroin are prescribed almost universally for the relief of pain. However Rees and associates showed a fall in mean aortic pressure 20 minutes after intravenous administration of 100 mg of pethidine. They did not consider pethidine to be the ideal drug for the relief of pain. MacDonald and co-workers observed a fall in mean aortic pressure after heroin. Thomas and colleagues[8] and the Lal group[4] encountered hypotension after morphine. Keats and Telford[9] showed that pentazocine, though comparable in analgesic potency to morphine, did not produce hypotension. Lal and associates[4] therefore studied its use in the treatment of infarction and showed that in 10 patients with myocardial infarction given pentazocine, 60 mg intravenously there was a significant increase in both systolic and diastolic arterial pressure 10 minutes after the injection, the mean systolic pressure having risen from 128 mm. Hg to 144 mm. Hg ($p<0.01$) and the diastolic from 75 mm. Hg to 82 mm. Hg ($p<0.05$). The mean heart rate also increased from 84.9 per minute to 95.8 per minute ($p<0.01$). Although the drug produced some respiratory depression (fall in respiratory rate and minute ventilation and a rise in the arterial CO_2 tension), yet it probably improved the efficiency of the gas exchange (decrease in V_D/V_T ratio and A-a oxygen gradient). The mean arterial oxygen tension decreased from 64.9 mm. Hg to 60 mm. Hg. This fall in pO_2, although significant ($p<0.01$), does not seem to matter in practice, as Lal and associates,[10] in a separate study showed that administration of pentazocine had little effect on Pa_{O_2} when oxygen was being administered, and its use as an analgesic does not interfere with the proper oxygenation of the patient.

A leading article in the British Medical Journal concluded "that while newer methods of analgesia are certainly needed, in general practice morphine seems likely to retain its important place in the treatment of acute myocardial infarction."[11] Herxhberg, however wondered if morphine or other analgesics really deserved a primary role in coronary care therapy. He suggested that patients admitted to a coronary care unit with perhaps only a 10 per cent reduction in viable myocardium could continue to lose myocardial tissue from further ischemia unrecognized because of the administration of morphine. Lal and associates[4] showed an increase of V_D/V_T ratio and A-a gradient after morphine in a small number of patients. Possibly therefore, hypotension, hypoxemia, and even the metabolic acidosis caused by morphine is partly responsible for the syndrome described by Herxhberg.

This work suggests that further considerations

should be given to pentazocine and similar drugs it could be as useful to study the effect of such drugs on gas exchange in the lung as on hemodynamics.

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Corneal arcus in the Ugandan African

Corneal arcus (arcus senilis, arcus lipoides corneae)[1-3] has been variously associated with atherosclerosis,[11,12,14] hypercholesterolemia,[11,3] aging,[4] diabetes mellitus, endocrine disease and vitamin deficiencies. The association between corneal arcus and arterial disease, and especially coronary atherosclerosis, has been found by many[4,11,3] but not all investigators.[6,12] Corneal arcus has also been shown to be common in the Zambian the American Negro[9] and the Aleut of southwest Alaska in none of these groups has an association with arterial disease been noted

The present investigation was undertaken to establish the incidence of corneal arcus in a group of Ugandan African patients and to attempt to associate its occurrence with cardiac disease and serum cholesterol, and also with age, sex, tribe, and serum protein levels. Atherosclerosis and coronary artery disease are extremely rare in the Ugandan African.[17]

One hundred consecutive patients admitted to one medical ward at the Mulago Hospital, Kampala, were studied Detailed questioning was used to obtain a history with particular reference to the cardiovascular system. A full clinical examination, including a blood pressure recording and retinal examination, was made. Assessment of the presence of arcus was made by naked eye in good daylight and also by torch light, and was graded 0, 1 2, and 3 (0 = absence of any evidence of arcus 1 = definite incomplete ring of translucence at the periphery of the cornea with a clear ring separating it from the limbus 2 = moderate sized ring with a clear ring separating it from the limbus 3 = very marked dense ring with no clear cornea between the ring and the limbus). Chest x-rays and electrocardiograms were performed on all patients. Serum cholesterol was measured in 98 patients.[18] Serum total proteins and electrophoresis, bilirubin alkaline phosphatase, glutamic oxaloacetic transaminase and hemoglobin were estimated in most of the patients by standard techniques.

The study included 60 male and 40 female subjects. The mean ages were 37 (range 10 to 70) and 36 (range 10 to 70) years, respectively The correlation between the presence and grade of arcus and stated age is significant ($= +0.550$ $p < 0.001$ $n = 100$) Five patients with arcus were below 20 years and 2 of those were 10 years old There is no significant difference in the sex incidence of arcus (Table I) Sixty nine of the patients were from the local Baganda tribe, 19 were immigrants from Rwanda and 12 were from Nilotic or Hamitic tribes there is no significant difference in the incidence of arcus between these tribal groups.

There was a wide range of diagnoses. Eight of

Table I. Incidence of corneal arcus in the different sexes and age groups

Sex, age (yr.)	Grade of corneal arcus (see text)				
	0 (absent)	1	2	3	Total
Male					
10–30	14 (23.3%)	7 (11.7%)	3 (5.0%)	0 (0%)	24 (40.0%)
31–50	8 (13.3%)	10 (16.7%)	7 (11.7%)	2 (3.3%)	27 (45.0%)
51–70	1 (1.7%)	1 (1.7%)	7 (11.7%)	0 (0%)	9 (15.0%)
All ages	23 (38.3%)	18 (30.1%)	17 (28.4%)	2 (3.3%)	60
Female					
10–30	8 (20.0%)	9 (22.5%)	2 (5.0%)	0 (0%)	19 (47.5%)
31–50	4 (10.0%)	4 (10.0%)	5 (12.5%)	0 (0%)	13 (32.5%)
51–70	0 (0%)	0 (0%)	5 (12.5%)	3 (7.5%)	8 (20.0%)
All ages	12 (30.0%)	13 (32.5%)	12 (30.0%)	3 (7.5%)	40
Totals	35	31	29	5	100

31 (25.8 per cent), 9 of 29 (31.0 per cent), and 3 of 5 (60.0 per cent) of the patients with Grade 1, 2, and 3 corneal arcus, respectively, and 6 of 35 (17.1 per cent) without arcus had evidence of cardiovascular disease. In only one patient, with Grade 3 arcus, did this have an ischemic origin. This difference between patients with and without cardiac disease is not significant ($\chi^2 = 2.95$, $p < 0.30$). One 40-year-old patient with Grade 3 arcus had evidence of ischemic myocardial disease on the electrocardiogram. Three patients had conduction defects. Two of these (aged 70 and 54 years) had left, and one (aged 70 years) right bundle branch block. Two of these had Grade 3 arcus. Cardiomegaly was shown on the chest x-ray in 16 patients. In no case was aortic calcification present. There was no relation to the presence or degree of hypertension. Other diseases were also evenly distributed between patients with the various grades of arcus. Four of 35 (11.4 per cent) patients without arcus, and 3 of 31 (9.7 per cent), 21 of 29 (72.4 per cent), and 4 of 5 (80.0 per cent) of the patients with Grade 1, 2, and 3 arcus, respectively, had gray hair.

The relationship between the presence and grade of arcus, and the serum cholesterol level is not significant (= − 0.186, $p < 0.10$, = 98). The mean serum cholesterol was 142 (72–275) mg. per 100 ml. in the male patients, and 152 (77–360) mg. per 100 ml. in the female. The mean cholesterol level in the 51 to 70 year group was 141 mg. per 100 ml., and in the 10 to 30 year group, 146 mg. per 100 ml. There is not a significant correlation between the presence and grade of corneal arcus and the individual hemoglobin levels (= + 0.122, $p > 0.10$, = 95) or between corneal arcus and serum albumin (= + 0.073, = 99), or total globulin (= − 0.122, = 97). The correlation between serum γ-globulin and corneal arcus is, however, significant (= + 0.217; $p < 0.05$; = 97). The mean hemoglobin was 11.3 (2.2 to 17.6) Gm. per 100 ml., serum albumin 2.6 (0.6 to 4.2) Gm. per 100 ml., total globulin 4.1 (2.2 to 6.3) Gm. per 100 ml., and γ-globulin 2.1 (0.3 to 4.3) Gm. per 100 ml. There is no significant relationship between corneal arcus and serum bilirubin, alkaline phosphatase, or glutamic oxaloacetic transaminase.

A very high incidence of corneal arcus (65 per cent) has thus been shown in these 100 Ugandan African patients. This proportion is the highest so far reported in any population group. Although there was a significant relation to increasing age, the condition was present in 5 patients of less than 20 years, of whom 2 were only 10 years of age.

No significant difference in the sex incidence has been shown in this study and this differs from other reports, which have shown a male predominance.[1,8,11] Our numbers were small, however. In the Aleut, in whom arcus occurs at an early age and is not associated with cardiac disease or raised serum cholesterol levels, which is similar to the situation in our patients, a higher male incidence of the condition also exists.

The cause of the corneal arcus in our patients is unknown. The composition of the deposit has not been analyzed and may be different from that of European patients in whom an association with ischemic cardiac disease has been shown. There was no association in our patients with cardiac disease or high serum cholesterol levels. A significant correlation of the presence and degree of arcus has been shown to occur with the height of the serum γ-globulin. This could indicate that an infectiv… process, e.g., malaria, is relevant in its etiology. There was no evidence in our patients of local trauma or of trachoma. A dietary factor has not been eliminated. It seems likely, in view of the recently reported high incidence in the American Negro[5] and the Zambian African, that the Ugandan

African population is genetically predisposed to this condition.

Although corneal arcus may suggest hypercholesterolemia and ischemic cardiac disease in young European and American men,[10,11] racial and geographic factors clearly must be carefully taken into account

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Looped intra-atrial lead A knotty problem*

Knotting of flexible wires being used to record intracavitary electrocardiograms from the right atrium has been reported.[1-4] Four instances of knotting of a flexible wire electrode around a permanent pacemaker catheter have also been reported [5] These four episodes occurred at the time of placement of the permanent catheter after temporary pacing had been effected by the flexible wire electrode. The passage of a large lumen catheter over the wire up to the knot has not been reported as a technique to aid in removal of the knotted wire. The catheter may be used to push the knot back to the tip of the wire or to dilate the venous valves adequately so that the knot will not catch on the val es.

*Written while Dr. McGarrey was supported by Postgraduate Training Grant HE 5776.

This technique was used in a patient in whom the flexible wire* became knotted while attempting to record an intra atrial lead. This knot could be withdrawn to the supraclavicular area, but in spite of firm traction and maneu ering could not be withdrawn beyond this point. A No. 8 Cournand catheter was threaded over the wire into the vein in an attempt to slip the catheter over the knot or to push the knot back to the tip of the wire. Although the catheter would not go over the knot, it came to rest firmly against it, and it was possible to withdraw the catheter and the wire by direct traction.

*Flexile electrode ½ inch platinum probe ith stainless multistrand Flamoa steel, Teflon insulated, 60 inches, 12340-60. Davis & Geck, American Cyanid Company Danbury Conn.

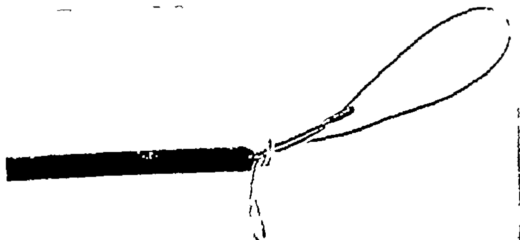


Fig. 1 Knotted platinum electrode with Cournand catheter passed to knot illustrating technique for removal in this patient.

The wire was noted to have a figure-eight knot at the distal end when it was removed (Fig. 1).

Knotting of flexible wires should be prevented by the use of portable fluoroscopy units at the time of wire passage and by immediate withdrawal of the wire if it should enter the right ventricle. If knotting of the wire does occur the technique described may be of benefit in removing the wire.

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This is interesting

As indicated previously spontaneous naturally occurring phenomena unfold before us which answer important questions in biology or at least introduce thought-provoking concepts concerning biologic processes and medicine. As with the relationship of arterial pressure to coronary arteriosclerosis in aberrant coronary arteries, congenital corrected transposition of the great vessels of the heart displays a phenomenon which is interesting For example, it is a fact that patients with corrected transposition of the ventricles can live a normal life expectancy Thus, the right ventricle can carry the pressure, volume work, and power loads usually carried by the left ventricle without any difficulty The right ventricle does hypertrophy to a satisfactory extent, but it still maintains all the morphologic characteristics of a right ventricle. On the other hand, if a patient develops pulmonary hypertension with pressure levels no greater than that normal for the aorta, the patient develops the manifestation of cor pulmonale, usually develops serious difficulties, and even death can follow Therefore, the pressure load on the right ventricle cannot be the most important problem in cor pul-

monale. What is, then? The answer remains unknown. It may be related to the pulmonary vascular disease, associated respiratory diseases or the abnormally high pressure in the pulmonary arterial system and the associated factors involved in the pulmonary hypertension but it must not be dependent only on the work load of the right ventricle. The coronary circulation to a right ventricle carrying a high pressure load in cor pulmonale and a right ventricle carrying a high pressure load in corrected transposition of the ventricles also need consideration.

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Book reviews

THROMBOSIS, Division of Medical Sciences National Research Council. Edited by Sol Sherry Kenneth M. Brinkhous, Edward Genton, and James Stengle, Washington, D. C., 1969 National Academy of Sciences, 762 pages. Price $12.50.

Thrombosis continues to offer considerable difficulties in the practice of medicine. The physician would like to control thrombus formation with anagents to his patient so that he can encourage it when necessary and prevent it at other times. Through the auspices of the Division of Medical Sciences of the National Research Council, an extremely interesting and important conference was held in Washington, D. C., during late November 1967. The editors of the proceedings provide others with an excellent presentation of the conference. Thus, those who did not attend the conference have access for leisure review of the discussions. The participants included investigators and clinicians who are actively concerned with thrombosis. This book includes six parts covering aspects of the clinical spectrum, epidemiology nature of the thrombus, pathogenesis, hypercoagulability and fibrinolysis, and therapeutic considerations. The many papers dealing with selected aspects of the above six main problems are of interest and summarize the work and thoughts current in November 1967. This is a very useful review of thrombosis. It should interest all physicians especially those involved in investigations and management of thromboembolitic disease states.

CROTALARIA SPECTABILIS, The Pulmonary Hypertension Plant. By J. M. Kay M.D. M.C.Path., and Donald Heath, M.D., Ph.D., M.R.C.P. M.C.Path., Springfield, Ill., 1969 Charles C Thomas, Publisher 146 pages. Price $12.00.

Drs. Kay and Heath review very all the interesting syndrome of pulmonary hypertension produced in rats by the seeds of the leguminous plant, *Crotalaria spectabilis*. The authors describe the plant and its alkaloids and the pathologic effect on the pulmonary vasculature, the heart, and lungs of rats that are fed the seeds. The hypertension produced is discussed along with the role of mast cells and serotonin. Even though this is a highly specific entity the possible use of this phenomenon toward better understanding of pulmonary hypertension and its management makes this book of considerable value. Everyone engaged in pulmonary vascular physiology and study of pulmonary hypertension will find this book useful. The authors have rendered a service to medicine by their monograph.

ATLAS OF ARTERIOGRAPHY IN OCCLUSIVE CEREBROVASCULAR DISEASE. By Jorge Weibel and William S. Fields, Philadelphia, 1969 W. B. Saunders Company 190 pages. Price $19.00.

As the title indicates this is truly an atlas consisting of photographic reproductions of clinical cervical and cerebral angiograms of patients with varying degrees of *arterial occlusive* disease. Each angiogram is accompanied by an artist interpretation in clear line drawings. The illustrations and drawings are excellent as well as the text or legends describing the essential features of work. Radiologists, neurologists, vascular surgeons, and cardiovascular physicians will find this valuable atlas to study and own. The atlas, of course, does not indicate the degree of impairment of cerebral circulation resulting from the occlusive lesions recorded. The functional disturbance is left to the imagination of the reader. The clinician, through experience, estimates the importance of these obstructive lesions once they are defined by arteriography. The atlas contains a discussion of techniques and clinical indications and contraindications for cerebral arteriography. With increasing interest in and use of cerebral arteriography this fine atlas is of value to clinical practice.

BEDSIDE CARDIOLOGY. By Jules Constant, M.D. Boston, 1969 Little, Brown & Company 347 pages. Price $12.50.

Doctor Constant book on bedside cardiology consists entirely of questions and answers related to symptoms and signs obtained at the bedside of the patient. The questions raised and answered are good, practical ones. The answers are brief but do not always answer the questions properly. For example, on page 41 the author says the carotid pulse wave is due more to flow than pressure. This is not clear to this reviewer. Does the author mean the kinetic force associated with flow? If so, is this force more important than the dynamic force exerted radially? Although most of the questions raised seem to be simple to answer many answers remain unknown, as Dr. Constant indicates, but many are only partially answered by the author. The illustrations are simple, fairly numerous, and helpful. The reader will find this to be an interesting book and an interesting approach to the discussion of bedside problems, which should be useful to doctors and medical students for critical and provocative reading.

Announcements

The American Society for Testing and Materials announces the meeting of Committee F-4 on Surgical Implants, May 6 to 8, 1970 at Battelle Memorial Institute, Columbus, Ohio.

The Argentine Federation of Cardiology a scientific entity which comprises all the cardiological societies of the interior of the country will hold its third national congress in Cordoba, Argentina May 24 to 29 1970, under the auspices of the National and the Catholic Universities of Cordoba and the Ministry of Social Welfare.

For information write to the Secretary of the Third National Congress of Cardiology Av Colon 637 Cordoba, Argentina.

The Fourth Annual Workshop in Electrocardiography sponsored by the Rogers Heart Foundation, will take place at the Princess Hotel, Hamilton Bermuda, from June 8 through June 13 1970. The workshop's director is Henry J L Marriott, M D

For further details write to the Rogers Heart Foundation, St. Anthony's Hospital, St. Petersburg, Fla.

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Editorial

Priorities and dilemmas in medical care

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A few years ago I remarked to my young intern that I had the impression when going around the wards that I remembered more about the patients than he did in spite of the fact that I made only two ward rounds each week and visited several other hospitals. He thought the explanation was that I remembered the things that interested me and he remembered the things that interested him. I asked him what were the things that interested him, to which he replied "Oh, academic things," and when I asked what academic things, he replied again "Oh, anything academic." I then reminded him that when I had appointed him to be my intern I had told *him that he would be* leaving the rarified atmosphere of his teaching hospital professorial unit and that he would have to deal with the bread and butter medicine of a community hospital. Furthermore, my patients were interested not in academic things but in practical things, and the practical things that interested them most were to know what was wrong, what was the treatment, and *how soon* they would get better. He replied that I need not worry because given another three months, he would be all right. And of course he was, succeeding in his specialist examinations and gaining an appointment to a metabolic unit.

But this is surely the major problem of modern medicine. The patient can easily get lost in the scientific complexities of the case, or as Sir Francis Walshe[1] said in 1950 in his Linacre lecture entitled "Humanism, History and Natural Science in Medicine," he had a "conviction that to rebuild a bridge between medicine and the humanities is a pressing need, that the building can be done only from the side of medicine, and that someone must make a start if medicine is not to lapse into a mere congeries of techniques, to fail in coherence on its theoretical side and to suffer the loss of its traditional values." He recalled that one of Linacre's last acts had been to *found the Linacre lectures at St. John's* College, Cambridge, expressing in his Deed of Gift the wish that they should "resound to the Glory of God, the true art of medicine, the relief of the fallen, and the increase of the realm." *How* relevant that wish remains today and how bewildered Linacre might be if he were to walk into the lecture theatre at the Royal College of Physicians, which he founded in 1518, and were to hear the presentation of a modern scientific paper. Since 1950, the pace of scientific medicine has quickened almost beyond belief and the public conscience has become aroused on many counts.

Two outstanding problems are how the

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benefits of such major advances as transplant surgery and other life saving techniques such as chronic hemodialysis should be rationed and how the escalating cost of modern medical care should be shared—or even contained

Although the idea of rationing medical care is objectionable it was pointed out by Powell[8] that the distribution of any expensive commodity in short supply will inevitably be rationed either by cost or by the availability of appropriately trained manpower and in each respect modern medical care can be no exception In Britain the National Health Service was introduced to ensure that no one should be denied essential medical care for lack of financial resources. But this does not mean that every patient who might benefit from chronic hemodialysis can obtain a place on a dialysis program let alone everyone who might benefit from a spare kidney heart or liver receive one For there is of course a Treasury ceiling on health expenditure and the Planning Unit of the British Medical Association under the chairmanship of Professor Henry Miller has recently examined the problems of financial priority raised by the development of new and complex methods of treatment at a time when the total resources devoted to medicine are insufficient to make even the treatments of established value freely and promptly available to all who need them

In its report[3] the unit points out that it has been estimated that about 2 000 lives in Britain could be saved each year if long term dialysis facilities were available. This would cost £30 million each year together with the services of about 10 000 skilled personnel Renal transplantation at an estimated cost of £6 000 per patient must be regarded as a better investment, and the expansion of the present renal transplant program appears to be a matter of urgency both on humane and financial grounds Further research into the technical and scientific problems of cardiac transplantation and liver transplantation is clearly required but the Planning Unit rejects the view that organ transplantation and similar complex methods of treatment should be discouraged in the dubious expectation that this would lead to much needed improvements in the quality or quantity of existing services.

On the other hand the Planning Unit believes that more should be done to exploit the knowledge we have already gained in the field of preventive medicine and suggests that if a massive campaign against the cigarette met with even modest success it would probably save more lives at present sacrificed to lung cancer coronary thrombosis and chronic bronchitis than many more dramatic curative procedures.

It also suggests that existing services and methods should be reviewed and asks for instance whether patients with hernias or varicose veins really do better when treated by a long stay in hospital than those given only a short stay or even out patient treatment. Similarly does the patient with cardiac infarction do better under the continuous monitoring of the coronary care unit than he would do in bed at home with simple nursing care and at what point does population screening cease to pay dividends and become counter productive?

These are challenging thoughts and questions and they aroused considerable comment in the lay press. *The Times*, London[4] in a leading article entitled 'The Cost of New Hearts acknowledged that the report was shrewd and sensible but criticized it for being superficial because of the inability of the Planning Unit to appreciate the financial dilemma of the Health Service The report had stated that over all expenditure on medicine in Britain is well below that in most other developed countries and called for a substantial increase in the financial allocation to the National Health Service. But *The Times* claims that it is not practical politics to expect any substantial increase in the amount of tax revenue devoted to the Health Service for some years to come and considers it necessary to seek other sources of money for the British medical system and to consider more rigorously the proper priorities for expenditure within the service so that the right balance may be achieved between extending the range of medical skills and applying those which already exist.

Surely the leader writer is echoing what

Sir Francis Walshe said so eloquently in his Linacre lecture, and surely the problems of priorities and dilemmas in medical care are not new but only more complicated. Some years ago the Rev. Dr. W. L. Sperry,[5] who was then Dean of Harvard Divinity School spoke to the staff of the Massachusetts General Hospital on "Moral Problems in the Practice of Medicine." In the course of his address he recalled that Dr. Schweitzer had spent part of the time on one of his African journeys in thinking out some basic ethical principle. One day while the party was making its way through a herd of hippopotami there flashed upon his mind the phrase Reverence for life—for all life. Dr. Sperry suggested that many dilemmas could be resolved by thinking of that phrase and by a willingness to take time and trouble with individuals at the expense of that abstraction known as mass man. Much emphasis is laid today on the importance of team work in medical care but in the worst medical crises the patient often looks desperately for one person on whom he can rely and the threatened submergence of the personal physician in favor of the team may make this person difficult to identify. A senior colleague once said that his most humbling experience had been when a dying patient had told him that when he came into his room it was like a light shining in the darkness. Surely this is testimony enough to the enduring need for a personal physician not only with a reverence for life, but with the ability to see the wood for the trees in this day of complex scientific medicine.

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Clinical communications

Bundle branch block in acute myocardial infarction

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Considerable interest has been shown during the last few years in conduction disturbances following acute myocardial infarction and this has been stimulated by the study of arrhythmias during continuous electrocardiographic (ECG) monitoring[1] and the treatment of atrioventricular (A V) block with endocardial pacing[2] There has been much discussion on the role of pacing in acute infarction and a number of workers have agreed that all patients with second or third degree A V block should be paced or should have a pacing electrode inserted into the right ventricle and attached to a demand pacemaker[3-6] Less attention has been paid to the prognostic significance of bundle branch block and its relation to A V block although its incidence and natural history have been described[7-10]

The present study of the incidence and prognosis of bundle branch block was made as a result of a previously reported survey[11] in which important differences were described between the natural history of A V block according to whether it complicated anterior or posterior infarction It was found that A V block in posterior infarction often progressed from first to second degree and occasionally to third degree Stokes-Adams attacks were uncommon, the prognosis from the A V block itself was good and when complete heart block occurred the QRS complexes were usually of normal duration indicating a high ventricular pacemaker In anterior infarction, on the other hand A V block was usually complete QRS duration was prolonged attacks of asystole (Stokes Adams attacks) were common the prognosis was poor and the warning of complete heart block in anterior infarction was not first degree heart block but right bundle branch block (RBBB) It was thought that these findings indicated that it was not necessary to treat most patients with posterior infarction and A V block with endocardial pacing It might be advantageous, however to pass an electrode catheter attached to a demand pacemaker in patients with anterior infarction and RBBB even if no A V block was present

In the light of these findings, a survey was made of all patients passing through a coronary care unit during a period of over two years in order to examine the incidence and prognosis of bundle branch block and to confirm the relationship between RBBB and A V block which had been found in cases of anterior infarction

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Results

During the period March 1967 to June 1969 565 patients with acute infarction were admitted to the coronary care unit at Green Lane Hospital.[14] No case selection was made except that most patients aged 70 years or over were excluded because of shortage of beds, and 5 per cent of the patients were referred from other hospitals because of some complication. This report thus refers to a relatively unselected group of patients. Myocardial infarction was presumed to have occurred when at least two of the following three criteria were satisfied (1) characteristic clinical presentation (2) pathological Q waves, S-T elevation or T wave inversion in the ECG with evolutionary changes (3) serum glutamic oxaloacetic transaminase (SGOT) over 45 units per milliliter on one of three successive days.

As well as routine 10 second ECG strips to show arrhythmias, daily 12-lead ECGs were done on all patients, while recently twice daily ECGs have been done on patients with anterior transmural infarction. Bundle branch block was defined according to the criteria of Goldman.[15] Particular attention was paid to the presence or absence of associated abnormal left axis deviation associated with right bundle branch block, as this has been shown to indicate additional block of the superior division of the left bundle branch.[16] Included in the patients with left bundle branch block (LBBB) were 3 cases of incomplete or atypical left bundle branch block,[16] 4 who showed the changes of inferior peri-infarction block with QRS widening to more than 0.12 sec, and one of anterior peri-infarction block with QRS widening.[16]

RBBB occurred in 38 patients (7 per cent of the total) and LBBB in 25 (4 per cent Table I). Thus the total incidence of bundle branch block was 11 per cent in this series. When patients referred from other hospitals were excluded the incidence of RBBB was 6 and of LBBB 5 per cent.

The mortality rate was high in both groups being 48 per cent in patients with LBBB and 61 per cent in cases of RBBB (Table I). Whereas LBBB was present on admission in all but 3 patients, RBBB developed during observation in over half the cases, and subsequently resolved in one third of the patients during their hospital stay. In all but two of the patients with RBBB the infarct causing it was anterior and transmural (acute myocardial infarction with pathological Q waves in the precordial leads). In one case, the infarct was anterior and subendocardial (S-T segment and T wave changes only), while in the other it was inferior and transmural. The site of the infarct associated with LBBB could not be determined except in those patients with peri-infarction block and QRS widening.

Complications which developed in patients with bundle branch block are shown in Table II. In addition to the complications listed nearly all patients were seriously ill and had cardiac failure or shock in some degree while the incidence of arrhythmias was higher than in patients not having bundle branch block. Ventricular fibrillation occurred in over 25 per cent of all patients with bundle branch block, the difference in frequency between

Table I Incidence and natural history of bundle branch block complicating acute myocardial infarction

Incidence	RBBB	LBBB
Total patients with BBB	38	25
Incidence %	7	4
Mortality	23 (61%)	12 (48%)
BBB present on admission ECG	15 (40%)	22 (88%)
BBB transient	14 (37%)	2 (8%)

Table II Complications in patients with myocardial infarction and bundle branch block

Complication	RBBB	LBBB
Complete heart block	10 (26)	2 (8%)
Asystole	13 (34)	0
Ventricular fibrillation	13 (34)	6 (24)

cases of RBBB and LBBB being insignificant There was a difference however between the incidence of complete heart block in cases of RBBB compared with patients having LBBB (RBBB 26 per cent LBBB 8 per cent) This difference was of borderline significance ($\chi^2 = 3.29$ $p<0.10$) Asystole developing suddenly and not as a terminal manifestation of heart failure or cardiogenic shock occurred in 13 patients with RBBB but in no patient with LBBB and this difference was highly significant ($\chi^2 = 14.6$ $p<0.001$) In 9 of these 13 patients asystole occurred in association with complete heart block

The mode of dying of patients with bundle branch block is shown in Table III There was a tendency for patients with LBBB to die of cardiac failure or cardiogenic shock, while patients with RBBB were more likely to die suddenly from asystole which was not reversed by resuscitation in 7 of the 13 patients in whom

Table III Mode of dying of patients with myocardial infarction and bundle branch block

Mode	*RBBB*	*LBBB*
Ventricular fibrillation	4	2
Asystole	7	0
Pump failure	3	0
Presumed arrhythmia	1	0
Cardiogenic shock	6	6
Cardiac failure	2	4
	—	—
	23	12

it occurred Resuscitation failed in 4 of the 9 cases in which asystole was associated with complete heart block and in 3 of the 4 patients in whom A V block did not occur

Factors associated with RBBB were next examined to see whether these were associated with a greater risk of asystole, complete heart block or death (Table IV) There was no evidence that the presence or absence of left axis deviation had any effect on prognosis regarding survival or the development of asystole though the prognosis tended to improve in patients who had transient RBBB

Autopsies were carried out on 18 of the 23 patients who died with RBBB and on 5 of the 12 who died with LBBB In all patients with RBBB the anterior descending branch of the left coronary artery or the left main coronary artery before its bifurcation was occluded or grossly narrowed by atheroma or thrombus. Infarction was extensive in all cases, and usually involved the anterior part of the left ventricular myocardium and interventricular septum In patients with LBBB extensive coronary atheroma was present but the finding of occlusion of the left anterior descending artery was less constant and the site of infarction was not constant

Discussion

The present findings of an incidence of bundle branch block of 11 per cent in acute infarction and the high mortality rate of over 50 per cent are in accord with those of previous workers.[7,8,10,14] Information in

Table IV Factors associated with complications in patients having RBBB

Complication	*Total patients*	*C H B*	*Asystole*	*Death*
L.A.D present	21	5 (24%)	6 (29%)	11 (52%)
L.A.D absent	17	5 (29%)	7 (41%)	12 (71%)
RBBB present on admission	15	3 (20%)	4 (27%)	9 (60%)
RBBB absent on admission	22	6 (27%)	9 (41%)	14 (64%)
RBBB transient	13	2 (15%)	2 (15%)	6 (46%)
RBBB in all cardiograms after onset	25	8 (32%)	11 (44%)	17 (68%)

C.H.B. = Complete heart block; L.A.D. = left axis deviation.
*Not known in one case.

previous literature about the prognosis of RBBB compared with LBBB is less plentiful, but Master and associates, and Bauer and associates[9] found an equally bad prognosis for both types of conduction defect.

Accurate information on the mode of dying and the incidence of asystole and complete heart block is necessarily incomplete in patients reviewed before the introduction of ECG monitoring. Bauer and associates[9] reporting on patients monitored in the coronary care unit at Sydney Hospital, found that patients with either type of bundle branch block were more likely to die from shock and heart failure, thus limiting the role of resuscitative measures. Hunt and Sloman[16] also do not comment on the respective modes of dying of monitored patients with RBBB and LBBB but state that advanced A V block, nodal rhythm, ventricular standstill and asystole were common in both groups. The present report, which deals with a larger series of monitored patients, suggests that patients with RBBB are more likely than those having LBBB to die from asystole developing in the course of complete heart block and not as a terminal manifestation of cardiac failure. The findings agree with a recent report, in which it was found that RBBB was commonly associated with complete heart block and sudden death in anteroseptal infarction and with several of the cases described in other published series.

It has long been known from autopsy studies that bundle branch block in infarction is associated with involvement of the interventricular septum. [20] In general previous workers have found no characteristic anatomical pattern of infarction associated with LBBB compared with that associated with RBBB nor of occlusion of any one coronary artery. Anatomical studies[21, 22] have shown that the proximal part of the right bundle branch is constantly supplied by a branch of the left anterior descending artery while the left bundle branch, which is a less discrete anatomical structure, derives its nourishment from septal branches of both right and left coronary arteries. This implies that RBBB would be commoner in cases of occlusion of the left anterior descending artery while LBBB might result from more generalized coronary atherosclerosis. The present findings of an association between RBBB and anteroseptal infarction the almost constant demonstration of proximal occlusion of the left anterior descending coronary artery at autopsy in these patients, as well as the less specific autopsy findings in cases of LBBB are in keeping with these studies. Other workers[7, 8] have not commented on this association though autopsy studies on relatively small numbers of patients reveal a trend toward an association between RBBB and occlusion of the left anterior descending artery. Support for the present observations also comes from the work of Blondeau and co-workers[24] who found necrosis of the right bundle branch to be a dominant feature in cases of anterior infarction complicated by complete heart block. Undoubtedly however the portion of heart muscle infarcted by a coronary occlusion is also determined by the pre-existing distribution of coronary disease so that a constant association between recent left anterior descending artery occlusion and RBBB would not be expected.[23]

The reason for the association of RBBB rather than LBBB with asystole and complete heart block is not clear. Though RBBB with left axis deviation in cases of atherosclerotic heart disease has been observed to be a frequent precursor of complete A V block,[24-26] this was not the case in this study which differs from these former series in being confined to patients with acute infarction. Left axis deviation implies block of the superior division of the left bundle branch and the lack of evidence that left axis deviation was a precursor of complete heart block and asystole in this study suggests that bilateral bundle branch block may not have been the mechanism. Another mechanism could be sudden extension of proximal RBBB to involve the main A V bundle. This could presumably result from part of the A V bundle taking its blood supply from the left anterior descending artery or from involvement of this structure by edema.

The reason for the transient duration of RBBB in many cases, compared with the

usual stability of LBBB is not clear but the possibility is suggested that RBBB was in most cases caused by the acute myocardial infarct whereas LBBB was usually a manifestation of pre-existing coronary atherosclerosis Insufficient in formation on the previous cardiographic status of patients who presented with in farction and LBBB was available for any estimate to be made of how long LBBB had been present and there was no im portant difference in the incidence of a history of previous ischemic heart disease between cases of RBBB and LBBB It is still likely however that LBBB was in many cases a chronic lesion and that if only the acute cases of LBBB could be considered the mortality rate would be at least as high as in patients having RBBB

The diffuse anatomical structure of the left bundle branch is reflected in less clear cut criteria for the ECG diagnosis of LBBB than is the case in RBBB The present series includes 8 cases of incomplete LBBB (3 with a QRS duration of 0 10 to 0 12 sec and 5 with peri infarction block and a QRS duration of over 0 12 sec) These cases were included as their course was no different from that of patients having complete LBBB and the correlation of incomplete LBBB with lesions of the left bundle branch has been established [13] It is probable that previous investigators have also included such cases as examples of LBBB

The therapeutic implication of the present findings is that asystole associated with complete heart block may be anticipated by the insertion of a transvenous electrode catheter attached to a demand pacemaker in patients with anterior transmural in farction who develop RBBB It is now the practice in our coronary care unit to do twice daily 12 lead ECG s on all patients with anterior transmural infarction and to instruct the nurses to look for QRS widen ing in the monitoring leads of these pa tients. If RBBB develops, demand pacing is carried out. Despite this measure how ever the mortality rate remains high and in only one patient with anterior infarction and complete heart block in this series could recovery be directly attributed to endocardial pacing Steroids have been found to be of benefit in heart block com plicating infarction [22] and a trial of steroids in addition to demand pacing is planned in patients with anterior infarction who de velop RBBB Autopsy studies suggest however that death in most cases is due to massive destruction of cardiac muscle caused by proximal occlusion of the left anterior descending coronary artery

Summary

The incidence and natural history of bundle branch block in 565 patients ad mitted to a coronary care unit were examined Right bundle branch block (RBBB) was present in 7 per cent of patients with mortality rate of 61 per cent and left bundle branch block (LBBB) in 4 per cent of patients (mortality rate 48 per cent) The majority of patients with RBBB developed it during the course of their acute infarction compared to those with LBBB in whom the lesion was more chronic RBBB was associated with a significantly higher incidence of asystole than LBBB This usually occurred during the course of complete heart block and was not a terminal manifestation of shock or cardiac failure The presence of left axis deviation did not adversely effect the prognosis of patients with RBBB either for survival or for the development of asystole RBBB nearly always developed during the course of anterior transmural infarction and autopsy in fatal cases showed proximal occlusion of the left anterior descending coronary artery as an almost constant finding The site of infarc tion could seldom be determined from the cardiogram in patients with LBBB and autopsies showed more generalized coro nary atheroma These results suggest that the use of a transvenous electrode catheter attached to a demand pacemaker should be considered in patients with anterior transmural infarction who develop RBBB

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Characteristics of innocent and stenotic cervical bruits

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Bozeman Mont

Many strokes are the result of stenosis in the surgically accessible neck arteries which supply the brain Physical examination of these arteries has become important with the hope that recognition of stenosis would permit treatment to prevent or limit cerebral infarction Hence it is important to recognize the presence of cervical bruits Unfortunately a cervical bruit also may be heard over a healthy as well as a stenotic artery which leads to a frustrating and uncertain diagnostic problem

It is possible to increase the efficiency and reliability of medical diagnosis through analysis by high speed computers. The purpose of this investigation is to determine if it is possible to differentiate between the innocent and the stenotic bruit by an analysis of the acoustical signal This paper reports an attempt to solve the problem by analyzing the auscultatory signal from 13 patients, 7 with an innocent bruit and 6 with a stenotic bruit Three major techniques are employed (1) statistical analysis (2) spectral analysis and (3) zero-crossing analysis

Data collection

A total of 133 samples of bruit noises were gathered from 13 individuals The 7 bruits which were considered innocent were discovered on incidental physical examination on individuals ranging in age from 12 to 24 years. None had cardiovascular or cerebral symptoms asymmetry of blood pressure or alteration of the carotid or brachial pulse In a previously reported study[1] of 4 296 consecutive office patients, such bruits were found in 14 per cent of presumably normal persons 10 to 19 years old

In 5 of the 6 patients with a bruit classified as stenotic, there was arteriographic or surgical demonstration of arterial narrowing The remaining patient with carotid artery stenosis had low blood pressure distal to the point of narrowing (low retinal artery pressure as measured by ophthalmodynamometry) together with intermittent

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symptoms of inadequate blood flow to that part of the brain served by the carotid artery.

Each sample is a digitized form of the auscultatory signal recorded by placing a contact microphone over the source of the bruit. The heart sounds are excluded from each sample. Typical samples are shown in Figs. 1 and 2.

Initial recording of the auscultatory signal was done with a Sanborn Model 572 M surface contact microphone and a good

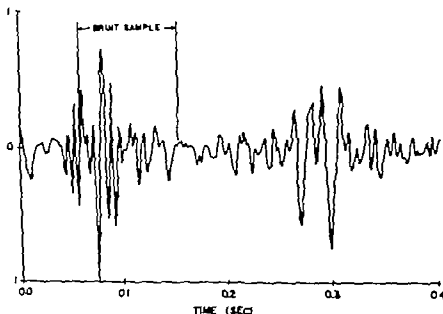


Fig. 1. First and second heart sound with innocent bruit.

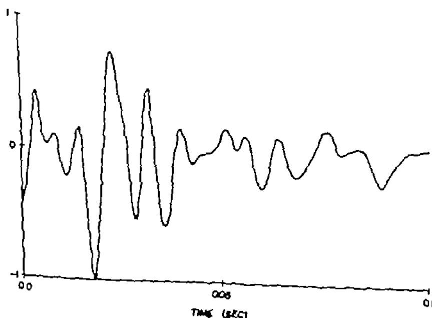


Fig. 2. Innocent bruit sample.

Characteristics of innocent and stenotic cervical bruits

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each spectrum The energy–mean frequency is defined here to mean that frequency which divides the signal energy equally Half of the energy in the signal is then present in frequencies above the mean and half below the mean The 90 per cent energy bandwidth is defined here to be that frequency band centered on the energy mean frequency encompassing 90 per cent of the signal's energy Equipment and sampling rates limit the frequencies studied to between 60 Hz and 200 to 500 Hz (depending on sampling rate)

t tests. *For each type of characteristic*, a t test was made between the innocent results and the stenotic results. This test shows the statistical reliabil ty of a given characteristic when the characteristic is used to distinguish between two populations. If a characteristic could possibly show dependence on population the t test again is used to compare each patient with each population

In determining a characteristic which will reliably separate the bruit families, false rejection of the null hypothesis which is that the two families are members of the same population must be minimized by setting the rejection level low—say at the 0 01 probability level Table I gives the results obtained using the t test to test the significance of the difference between the innocent mean and stenotic mean of six characteristics used in this study (1) variation (2) first moment (3) zero-crossing frequency (4) energy bandwidth (5) energy–mean frequency and (6) the number of major peaks in the energy density spec

Table I The t test of several bruit characteristics determining the validity of using the characteristic as a method of separating the stenotic and innocent bruit

Characteristic	Innocent mean	Stenotic mean	Degrees freedom	t test	Alpha probability
Histogram					
Variation	105090 0	107580 0	131	0 315	0 8
First moment	−707 5	−565 0	131	0 952	0 4
Zero crossing					
Frequency	175 3	273 5	131	9 000	
Spectral analysis					
Energy bandwidth	123 3	188 4	115	7 732	
Energy–mean frequency	82 0	130 7	115	7 604	
No of major peaks	5 23	7 55	112	5 577	

*Probability of [illegible] larger [illegible] less than 004

Table II *Diagnostic accuracy**

Characteristic used for test	Innocent bruits compared to		Stenotic bruits compared to		10 patients compared to	
	Innocent population ($p = 0.05$)	Stenotic population ($p = 0.01$)	Innocent population ($p = 0.05$)	Stenotic population ($p = 0.01$)	Innocent population ($p = 0.05$)	Stenotic population ($p = 0.01$)
Major peak count	86	57	83	100	85	77
Zero crossing frequency	67	50	67	83	62	62
Energy–mean frequency	43	57	50	83	46	69
90% Energy bandwidth	43	43	50	67	46	54

*Given in percentage of correct diagnoses.

quality musical type tape recorder Digitizing the conversation of the analogue (voltage) form of the signal to a digitized numerical form was done using an EECO 761 Analog to Digital Converter* at digitizing rates of 4 000 and 10 000 samples per second The analogue to-digital converter was controlled by a Model 921A Digital Controller †

Data analysis

Hypothesizing that the innocent bruit and the stenotic bruit belong to two different families of wave forms this study has as its objective the identification of the characteristics which may be used to differentiate between the two wave forms. When the differences are known a reliable more practical method of diagnosing stenosis can be established

In the computer analysis of the digitized samples four main approaches were taken (1) Visual examination was made of computer plots of the samples the histograms of the samples and the energy spectra of the samples. (2) The variation and first moment of the histogram of each sample was computed and examined (3) The signal s zero-crossing frequency was analyzed (4) The number of peaks bandwidth and center frequency of the energy-density spectrum were computed for each sample and the results were analyzed The plots were all normalized for ease of comparison A more detailed description of each approach follows.

Histogram analysis A histogram or frequency of amplitude distribution curve is a plot of the frequency of occurrence f of the amplitude versus the amplitude a The variation a common method for indicating histogram characteristics is given by the following relation

$$\text{Variation} = \sum^{N} f \ (a - a) \ /N$$

where N is the number of points or amplitude in the histogram and a is the mean amplitude given by

$$a = \sum_{=1}^{N} a_i f_i/N$$

The first moment of the histogram is given by

$$\text{First moment} = \sum_{=1}^{N} f_i \ (a_i - \bar{a})/N$$

and will show any characteristic difference in the symmetry of the two families of histograms.

Zero crossing frequency Zero crossing analysis has proved to be a simple highly accurate method of speech analysis[2] and of murmur analysis.[3] It is actually a rough form of spectral analysis and usually is done by a series of broad band filters whose outputs are all analyzed for amplitude zero crossings The zero-crossing analysis used here consisted of counting the number of times that the unfiltered bruit signal amplitude passed through its own average value—zero The number of crossings was divided by the sample period to give a bruit characteristic namely the pseudofrequency of zero crossing Unlike filtered analysis, this type of zero-crossing frequency analysis is unaffected by low level high frequency components of the bruit spectrum

Energy density spectrum Using Fourier transform techniques a wave form such as the bruit signal can be represented by a series of sine and cosine functions. The amplitudes of these functions determine the energy density spectrum a plot of energy density versus frequency Recent advances in computing science have provided the fast Fourier transform an efficient and powerful tool in signal analysis of short digital records The fast Fourier transform converts the discrete time series representation of a wave form to a discrete frequency series or spectrum Spectral analysis has proved successful[4] as a basis for identifying heart defects in children from the phonocardiogram signal

One type of analysis applied to the energy-density spectrum was to count the number of peaks which were equal to or greater than 10 per cent of the maximum peak in each spectrum In addition if the two bruit families are composed strongly of one frequency band and the center frequency or the bandwidth is different for each family then a distinction can be drawn by looking at the energy–mean frequency and the 90 per cent energy bandwidth of

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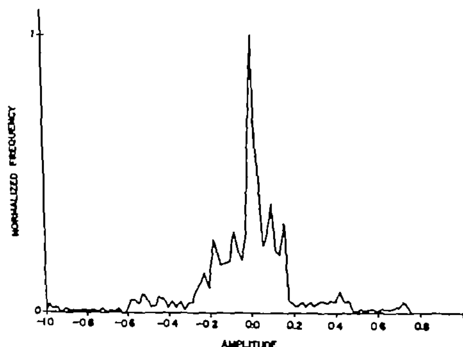


Fig. 3 Histogram of an innocent bruit sample.

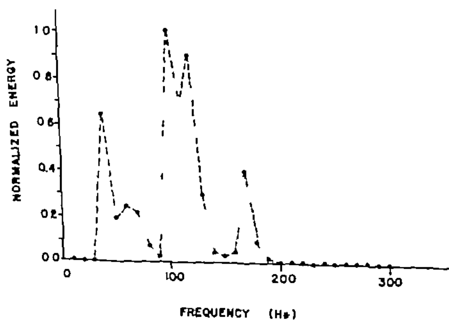


Fig. 4 Energy spectrum of an innocent bruit.

Table III Zero crossing energy–mean frequency and bandwidth averages for the two populations studied

Parameter	Innocent	Stenotic
Energy spectrum mean frequency	81 96 Hz	130 7 Hz
Energy-spectrum 90% bandwidth	123 3 Hz	188 4 Hz
Zero-crossing frequency	175 3 Hz	273 5 Hz
No of peaks in energy-density spectrum	5 23	7 55

trum While the first two characteristics were found not to be useful the probability for error in rejecting the null hypothesis is less than 0 001 for the last four characteristics.

In a t test between an individual and the innocent population the possibility of falsely accepting the null hypothesis must be minimized so the rejection level should be high say at the 0 05 level In a t test between an individual and the stenotic population the false rejection of the null hypothesis is the least desirable and the rejection level should be set low say at the 0 01 level In other words care must be taken so that a diseased artery is not judged healthy even at the risk of classifying some healthy arteries as diseased The reliability of using the four population–dependent characteristics to predict the type of bruit or condition of the artery is shown in Table II The percentages shown are obtained from the results of t tests between the patient means and the population means for each characteristic using the 0 05 and 0 01 rejection levels for the innocent population tests and stenotic population tests the patients are identified with the tabulated accuracies. The mean population values for the number of energy spectrum peaks mean frequency and bandwidth plus the mean population values for the zero-crossing frequency are given in Table III

Results

Examples of typical plots of the bruit sample bruit histogram and bruit energy density spectrum are shown in Figs. 1 through 5 Fig 1 is a plot of an innocent bruit wave form including the first and second heart sounds. A plot of the innocent bruit wave form sample of Fig 1 but, excluding the heart sounds, is shown in Fig 2 The histogram of the same bruit sample is shown in Fig 3 and its energy density spectrum is shown in Fig 4

Visual examination of the bruit waveform plots and of the bruit histograms of the sampled populations failed to reveal any outstanding differences between the stenotic bruit and the innocent bruit. On the other hand the energy spectrum plots of the innocent bruit population had on the average less peaks than plots of the stenotic bruit as can be seen by comparing Figs. 4 and 5 In general the visual examination of the results of the various methods of analysis did not prove reliable in the separation of the two types of bruits and it was therefore necessary to use the t test. The results of applying the t test to the various methods available for diagnosis are shown in Table II Since the results which are summarized in Table II may not be clear unless one is familiar with statistics, an example will be outlined

The following statements will deal only with the characteristic of major peak counts when this characteristic is used as the method for differentiation between the innocent and stenotic bruits. Similar statements can be made for the other methods by changing only the percentages of correct diagnosis. Suppose that a bruit sample is taken and it is unknown whether this bruit is innocent or stenotic If the bruit sample is innocent and the sample is compared with the innocent population mean then this bruit will be diagnosed as innocent 86 per cent of the time i.e a correct diagnosis. On the other hand if the bruit is stenotic and the bruit is compared with the innocent population mean then the bruit will be

spectrum) of the bruit. From the results of a t test, rejecting the null hypothesis at the 0.01 level, significant differences were also found between the following the mean zero-crossing frequency for stenotic bruits (273.5 Hz) and for innocent bruits (175 3 Hz) the average energy-spectrum mean frequency for stenotic bruits (130 7 Hz) and for innocent bru ts (82 0 Hz) the mean of the energy-spectrum 90 per cent band width for stenotic bruits (188 4 Hz) and for innocent bruits (123.3 Hz)

It is then possible to construct a reliable method of diagnosis for the cervical bruit based on the energy density spectrum Employment of additional analysis could considerably increase this reliability Such a method of diagnosis could employ recordings made by individual physicians and analyzed in a central location and/or a central facility to which patients would be sent.

It is also possible to construct an electronic system which would have as its purpose the analysis of or diagnosis of bru ts. For example instruments are commercially available which will produce the energy-density spectrum directly from the analogue signal from a contact microphone Using one of these instruments and the appropriate associated electronics, it would be possible to construct a system which could be used for the diagnosis of bruits either from a recording of the sounds or from a direct microphone input of the sounds from the patient. No method will be 100 per cent reliable, but the complementary methods of signal analysis, and the experience of the physician should lead to increased reliability in the diagnosis of cervical bruits.

*Mincor Real Time Spectrum Analyzer Signal Analysis Industries Corp 13 Di Tomas Court Copiague, N Y 726.

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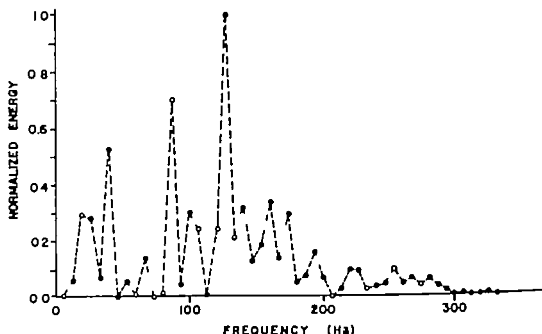


Fig 5 Energy spectrum of stenotic bruit

diagnosed as stenotic 83 per cent of the time If any sample either stenotic or innocent is compared to the innocent population the sample will be correctly identified or diagnosed 85 per cent of the time A random sample when compared to the stenotic population will be correctly diagnosed in 77 per cent of the cases A correct diagnosis can therefore be expected in from 77 to 86 per cent of the cases

Discussion

Experimental error was introduced into this study from three major sources (1) choosing the bruit sample (2) unknown frequency response of the arteries and body tissues during auscultation with a contact microphone and (3) the frequency limitations imposed on this study by the rate of analogue-to-digital conversion

While the authors fully realize that the microphone location blood pressure blood flow body position and acoustic coupling between the microphone and the source of the bruit can change the characteristics of the signal there was no attempt to control these factors in this investigation for the following reasons. The orientation of this investigation is toward a method usable by the practicing physician who may make the necessary recordings with available and inexpensive equipment Second there was little possibility that enough recordings could be made to determine the effects of microphone location and the characteristics of the tissue between the microphone and the bruit source on the recorded signal It was decided that these factors should be mixed indiscriminately and an attempt made to find a characteristic of the sound which was not adversely affected by these factors in the hope that identification of the stenotic bruit could still be made.

Only thirteen patients were examined However the statistical treatment of the data is valid for the number of samples used and it is felt that for the purposes of this investigation no further refinement of the data is necessary

Summary

The purpose of this study was to identify the stenotic and innocent bruit and to recognize possible identifying features of each Treating the acoustical signal as random stationary noise and examining the histogram for differences in variation the first moment was found to be unsatisfactory for differentiating between innocent and stenotic bruits. It was found that the two families of bruits could be reliably separated (with up to 85 per cent accuracy) by counting the number of major peaks in a periodogram (a form of the energy density

mines, vanillomandelic acid, creatinine, protein, and osmolality were measured in our own laboratories by methods previously described during the control period and then at weekly intervals throughout the study. An electrocardiogram, posteroanterior and left lateral chest roentgenograms, three-hour glucose tolerance test, urine culture, bromsulphalein retention, alkaline phosphatase, cephalin flocculation, and eyeground photographs were obtained at the end of the control, placebo, and drug periods. A rapid sequence intravenous pyelogram was obtained on all patients at the beginning of the study.

The experimental plan was to randomize the distribution of patients into two groups. In one group a control period of 4 days was to be followed by 14 days of intravenous placebo (consisting of 20 ml. of normal saline with 3.75 mg. nicotinic acid)* and then by 14 days of intravenous diazoxide injections (300 mg.); the alternate group was to have 14 days of diazoxide followed by 14 days of placebo injections. This was to be a single-blind experiment. The patients were to be continued on their prehospitalization medications until their diastolic blood pressures, as determined by 4 daily reclining and standing indirect measurements (10 A.M. and 2, 6, and 10 P.M.) taken according to a standardized protocol as described in other studies, warranted reduction in antihypertensive medication or until they developed symptoms of postural hypotension correlating with a decrease in diastolic blood pressure.

With the patients in the recumbent position, the injection was given as a rapid bolus (10 to 20 seconds). Blood pressure and pulse were recorded every minute for the ten minutes before and after injection. Recordings were repeated at 10, 20, 30, and 60 minutes and then every hour for the next 6 hours. Patients were required to remain recumbent for 2 hours after each injection.

Following discharge from the Clinical Research Unit each patient was seen in the Hypertension Clinic of the Presbyterian-University Hospital in one week and thereafter at monthly intervals until pretreatment blood pressures were again reached or until they required hospitalization for complications of their underlying disease.

Dropouts from the study caused distortion of the selection process and made the original plan to do a crossover statistical analysis unfeasible. Thus the data obtained were statistically analyzed using a paired t test comparing the last 3 days of diazoxide period with the last 3 days of placebo and also comparing the last 3 days of the diazoxide period with the last 3 days of control. One patient (No. 1) was not included in the statistical analysis as she was not studied on the Clinical Research Unit and lacked adequate metabolic control and protocol blood pressures.

Prestudy data for the 10 patients entering this investigation are presented in Table I. These patients had known hypertension from 9 months to 15 years and had been observed by us or one of our group from one month to 9 years. Each was considered to have severe hypertension inadequately controlled with oral medication either as clinic patients (Nos. 4, 5, 6, 9, and 11) or as hospitalized patients (Nos. 1, 2, 3, 7, and 8) whom we transferred to the study group. As can be seen, all patients presented objective evidence of hypertensive cardiovascular disease; 8 had funduscopic findings which warranted the opinion that their disease was in an accelerated phase.

Case reports

Patient 1 received 17 injections of 300 mg. of diazoxide over 17 days to maintain adequate lowering of diastolic blood pressure. During the time of injections this patient required bethanidine, 400 mg., Aldomet, 2 Gm., and chlorothiazide, 500 mg., daily. Only moderate control of the diastolic blood pressure was achieved. Her course was complicated by progressive cardiac failure and by sodium depletion and dilution. These problems were controlled and, upon completion of the diazoxide injections, she was maintained on bethanidine, 600 mg., Aldomet, 1 Gm., and chlorothiazide, 500 mg., daily until her death 7 days later from renal failure. No placebo therapy was given to this patient.

Patient 2 was given 11 daily injections of diazoxide with good control of his diastolic blood pressure and without the use of other antihypertensive medication during this period. The blood urea nitrogen fell from 101 to 68 mg. per cent, but there was no clinical improvement. The day after the last diazoxide injections he developed pulmonary edema and died 3 days

*Chosen to match the flushing sensation of rapid diazoxide injection.

Failure of repeated diazoxide injections to modify the course of severe hypertension

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The majority of reports dealing with the use of diazoxide as an antihypertensive drug have described its employment in acute hypertensive emergencies or to quickly lower elevated blood pressures prior to the institution of more chronic therapy. However, a report by Finnerty, Davidov, and Kakaviatos[1] proposed that repeated daily injections of diazoxide caused an amelioration of the hypertensive state that was longer than what might be expected from limited therapy. Further, their study suggested that such therapy achieved results rapidly and was virtually without side effects. Such an effect would represent a significant contribution to the treatment of hypertension, especially in patients with advanced disease. Accordingly, the present study was undertaken in an attempt to confirm these findings on a controlled basis where the previously demonstrated effects of hospitalization and placebo[2] could be separated from the effect of the drug.

Material and methods

Criteria for admission of a patient to the study included repeated diastolic blood pressures of 120 mm. Hg or more, at least Grade II funduscopic changes by the Keith-Wagener classification, and a willingness of the patient to remain on the Clinical Research Unit of the Presbyterian University Hospital for a minimum of 5 weeks. All patients were informed of the nature of the study, its implications, and the possible complications before they were admitted to the study.

Following admission to the Clinical Research Unit all patients received a complete history and physical examination. All patients were placed on individualized diets containing known amounts of sodium and potassium. Initial and then triweekly measurements of serum blood levels of sodium, potassium, chloride, carbon dioxide content, uric acid, and creatinine, as well as fasting blood sugar and blood urea nitrogen, were obtained from the Central Chemistry Laboratory of Presbyterian University Hospital. Blood levels of hemoglobin, the hematocrit, differential white cell count, reticulocyte count, and platelet count were obtained from the Laboratory of Presbyterian University Hospital; plasma free fatty acids and urinary levels of catechola

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mines, vanillomandelic acid creatinine, protein and osmolality were measured in our own laboratories by methods previously described[3] during the control period and then at weekly intervals throughout the study. An electrocardiogram posteroanterior and left lateral chest roentgenograms, three hour glucose tolerance test, urine culture bromsulphalein retention alkaline phosphatase, cephalin flocculation, and eyeground photographs were obtained at the end of the control placebo and drug periods. A rapid sequence intravenous pyelogram was obtained on all patients at the beginning of the study.

The experimental plan was to randomize the distribution of patients into two groups. In one group a control period of 4 days was to be followed by 14 days of intravenous placebo (consisting of 20 ml of normal saline with 3.75 mg nicotinic acid) and then by 14 days of intravenous diazoxide injections (300 mg)* the alternate group was to have 14 days of diazoxide followed by 14 days of placebo injections. This was to be a single-blind experiment. The patients were to be continued on their prehospitalization medications until their diastolic blood pressures, as determined by 4 daily reclining and standing indirect measurements (10 A.M. and 2, 6 and 10 P.M.) taken according to a standardized protocol as described in other studies,[4] warranted reduction in antihypertensive medication, or until they developed symptoms of postural hypotension correlating with a decrease in diastolic blood pressure.

With the patients in the recumbent position, the injection was given as a rapid bolus (10 to 20 seconds). Blood pressure and pulse were recorded every minute for the ten minutes before and after injection. Recordings were repeated at 10, 20, 30 and 60 minutes and then every hour for the next 6 hours. Patients were required to remain recumbent for 2 hours after each injection.

Following discharge from the Clinical Research Unit each patient was seen in the Hypertension Clinic of the Presbyterian-University Hospital in one week and thereafter at monthly intervals until pretreatment blood pressures were again reached or until they required hospitalization for complications of their underlying disease.

Dropouts from the study caused distortion of the selection process and made the original plan to do a crossover statistical analysis unfeasible. Thus the data obtained were statistically analyzed using a paired "t" test comparing the last 3 days of diazoxide period with the last 3 days of placebo and also comparing the last 3 days of the diazoxide period with the last 3 days of control. One patient (No. 1) was not included in the statistical analysis as she was not studied on the Clinical Research Unit and lacked adequate metabolic control and protocol blood pressures.

Prestudy data for the 10 patients entering this investigation are presented in Table I. These patients had known hypertension from 9 months to 15 years and had been observed by us or one of our group from one month to 9 years. Each was considered to have severe hypertension inadequately controlled with oral medication either as clinic patients (Nos. 4, 5, 6, 9 and 11) or as hospitalized patients (Nos. 1, 2, 3, 7 and 8) whom we transferred to the study group. As can be seen all patients presented objective evidence of hypertensive cardiovascular disease; 8 had funduscopic findings which warranted the opinion that their disease was in an accelerated phase.

Case reports

Patient 1 received 17 injections of 300 mg. of diazoxide over 17 days to maintain adequate lowering of diastolic blood pressure. During the time of injections this patient required bethanidine, 400 mg Aldomet, 2 Gm., and chlorothiazide, 500 mg., daily. Only moderate control of the diastolic blood pressure was achieved. Her course was complicated by progressive cardiac failure and by sodium depletion and dilution. These problems were controlled and, upon completion of the diazoxide injections, she was maintained on bethanidine, 600 mg., Aldomet, 1 Gm., and chlorothiazide, 500 mg., daily until her death 7 days later from renal failure. No placebo therapy was given to this patient.

Patient 2 was given 11 daily injections of diazoxide with good control of his diastolic blood pressure and without the use of other antihypertensive medication during this period. The blood urea nitrogen fell from 101 to 68 mg. per cent, but there was no clinical improvement. The day after the last diazoxide injections he developed pulmonary edema and died 3 days

*Chosen to [illegible] the [illegible] of rapid diazoxide [illegible]

Table I Background data—Diazoxide study

Patient	Race	Age	Sex	Duration HBP	Duration observed	Control period reclining			Control period standing			Fundi	BUN	Creatinine clearance	IVP	Heart size	ECG	Cardiac status
						S	D	M	S	D	M							
1 C D	C	29	F	6 yr	6 yr	230	172	191	200	156	171	IV	35	17		↑	LVH	Compensated
2, C B	N	41	M	10 yr	5 days	260	160	207	unable to stand			IV	101	10	N	\	LVH	0
3, G S.	C	48	M	9 mo.	6 mo.	200	150	187	160	120	140	IV	36	31	N	N	LVH	0
4 L. D	N	44	F	15 yr	5 yr	204	125	151	180	117	138	III	13	59	N	↑	N	Compensated
5, V M	N	46	F	10 yr	5 yr	256	131	173	239	133	171	III	12	72	N	↑	LVH	Compensated
6, W H	N	52	M	18 mo.	16 mo.	233	129	163	216	116	150	III	28	48	N	N	LVH	0
7 M P	N	49	M	15 mo.	1 mo.	210	150	170	170	130	143	III	35	20	N	↑	LVH	0
8, P J	C	60	M	8 yr	1 mo.	208	120	149	192	109	136	II	22	49	\	N	LVH	0
9, G. D	N	36	M	9 yr	9 yr	180	140	153	168	135	146	II	14	127	N	\	LVH	0
10 M R.	C	29	F	28 mo.	22.5 mo.	225	133	163	217	130	159	IV	19	49		↑	LVH	Compensated

Abbreviations HBP = High blood pressure S = systolic pressure D = diastolic pressure M = mean pressure N = normal, ↑ increased; 0 = no signs of failure; BUN = blood ea nitrogen IVP = intravenous pyelogram
*One kidney normal size other kidney absent.

later No placebo injections were given to this patient.

Patient 3 was given 14 days of placebo injections followed by 14 days of diazoxide. During the control and placebo periods, he required bethanidine averaging 7.5 mg per day until the start of diazoxide injections when the requirement for bethanidine dropped to 5 and then 2.5 mg daily Following the end of the injection period he was placed on Aldomet in doses up to 1 Gm. per day and Librium 15 mg daily He required digitalization 7 days after the end of injections for pulmonary edema. He was discharged only to be readmitted the following day in congestive heart failure with standing pressures ranging from 230/150 to 190/130. During the next 2 weeks he was maintained on bethanidine, 12.5 mg to 20 mg daily Intractable pulmonary edema developed and, although it partially cleared, increasing renal failure supervened and the patient died 28 days after the last diazoxide injection

Patient 4 received 16 days of placebo injections followed by 3 days of 300 mg of diazoxide. She entered the hospital on guanethidine 50 mg daily but by the seventh hospital day (first day of placebo) she was normotensive nd guanethidine was discontinued. Following the first injection of diazoxide she became unresponsive with weak, thready pulse and unobtainable blood pressure, all of which was immediately corrected with Trendelenburg positioning of her bed. On the ucceeding two days of diazoxide injection she had trancelike epi sodes but maintained an adequate blood pressure. She developed significant postural hypotension without complaints on all three days. Although part r all of her immediate response to diazoxide w thought to be primarily on a vasovagal basis, her psychological reactions and her normotension and her diabetic and cardiac status precluded further injections, and she was discharged from the hospital after only three injections. Eight weeks later in the clinic, her reclining pressure was 180/120 and tanding pressure 170/120, and guanethidine, 15 mg daily was instituted She was seen at monthly intervals with gradually increasing pressures on increased dosages of guanethidine. Seven months after diazoxide, she was admitted to Magee Women's Hospital for evaluation of a fibroid uterus. Again her blood pressure fell precipitously necessitating constant decrease in her guanethidine dose. When last seen in the clinic 10 months after diazoxide, her reclining and standing blood pressures were 210/140 and 165/120, respectively while on hydrodiuril, 25 mg and guanethidine, 20 mg daily At no time has there been progression of impairment n the target organs in this patient.

Patient 5 entered the hospital on guanethidine, 37.5 mg per day and reserpine, 0.1 mg. per day and underwent 15 days of placebo injection. Seven days of diazoxide injections then followed at which time she emphatically withdrew herself from the tudy Guanethidine was disco tinued after the first diazoxide injection and she was discharged on 0 1 mg of reserpine daily (She misunderstood her instructions and resumed her prehospital medications of guanethidine, 37.5 mg chlorothiazide, 500 mg and reserpine, 0.1 mg daily When seen one week later in the cl nic, she had pressures of 190/110 reclining and 170/85 stand g with symptoms of postural hypot nsion, and guanethidine was discontinued) N ne months after diazoxide her pressures were 240/120 tand g while on chlorothiazide, 500 mg and reserpine, 0.1 mg daily This patient had had four previous Presbyterian-University Hospital admissions, two of them of the Clinical Research Unit in connection with the evaluation of other drugs. Following each of these dmissions her blood pressure remained nder control with less medication than previou hospitalization levels for periods varying between 3 to 6 months.

Patient 6 entered the hospital on 37.5 mg. of

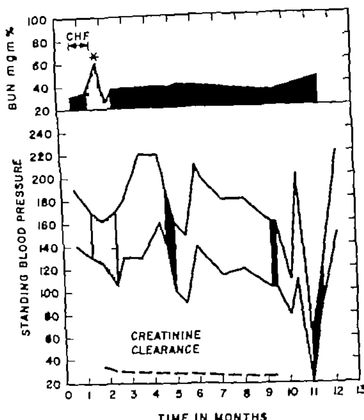


Fig. 1. Clinical course of Patient 7 since hospitalization for diazoxide therapy. The black areas on the blood pressure diagram represent periods of hospitalization. The speckled area represents the period of diazoxide injection. The asterisk indicates the period when the patient was febrile and suspected of having drug reaction to phenothiazines.

guanethidine daily which was discontinued on the second of 14 days of diazoxide injection. No placebo injection period was given to this patient because of marked erosions and resultant thrombophlebitis of the superficial veins in both arms. He was restarted on guanethidine, 12.5 mg. on the third day after starting diazoxide and discharged on this dosage. A month later he returned to the clinic with pressures of 240/150 reclining and 210/130 standing, and chlorothiazide, 500 mg. daily was added to his schedule. Two months after diazoxide he presented in the emergency room with high pressures and pulmonary edema. He was digitalized and his daily dosage of guanethidine increased to 25 mg. Three months after diazoxide his guanethidine was increased to 37.5 mg. daily and he was readmitted to the hospital for hematuria with standing blood pressure of 274/154, cardiomegaly, Grade III fundi, and a higher plateau value for his renal failure. No stone was seen or passed. Following discharge, he did poorly with progressive weight loss and renal failure, high pressures, intermittent hematuria, and sodium balance problems, despite increasing dosages of guanethidine. He was readmitted for his final hospitalization 7½ months after diazoxide with hematuria, microangiopathic anemia, and signs and symptoms of congestive heart failure, but with fair control of his blood pressure. He died 6 weeks later from progressive renal failure.

Patient 7 was transferred to our study on hydrochlorothiazide, 100 mg., guanethidine, 37.5 mg., reserpine, 0.25 mg., and Aldomet, 1.5 Gm. daily. His initial 13 day course of placebo injections was complicated by an allergic response to one of his previous medications, probably Thorazine, and later by the appearance of congestive heart failure and urinary tract infection. All of his antihypertensive medication was discontinued while the patient was on placebo due to the marked drop in his blood pressure. He developed (new) fever the last four days on diazoxide which abated when the injections were stopped. (Urine cultures at that time were sterile, but a week later again grew out *Streptococcus faecalis*.) He was discharged from the hospital on hydrochlorothiazide, 50 mg. daily and had pressures of 220/130 reclining and 180/130 standing when seen one week later. He continued to do poorly in spite of increasing antihypertensive medications and 10 weeks after diazoxide was readmitted to the Pittsburgh Oakland Veterans Administration Hos-

pital with pressures of 250/170 reclining and 220/160 standing, new exudates in his fundi and complaints of increasing visual disturbances and frequency of headaches. Guanethidine, 50 mg., and hydrochlorothiazide, 50 to 100 mg., were given daily. This was the first of five readmissions to the Veterans Administration Hospital: three were for signs and symptoms of hypertension and two for postural hypotension. During this time there was some diminution of renal function as seen by progressively decreasing creatinine clearances. When last seen 11 months after diazoxide therapy, he had pressures of 250/140 reclining and 220/150 standing while on Apresoline, 25 mg., and guanethidine, 25 mg., daily. His course is illustrated as Fig. 1.

Patient 8 entered the study on chlorothiazide, 500 mg., and guanethidine, 50 mg., per day. He received 14 days of diazoxide injections followed by 14 days of placebo injections. Guanethidine and chlorothiazide were discontinued by the fourth day of diazoxide therapy. Chlorothiazide, 250 mg. daily, was reinstituted on the fifth day of therapy and later raised to 500 mg. daily for the control of fluid and sodium retention. Guanethidine, 25 mg. per day, was restarted on the thirteenth day of therapy. He was discharged on these medications and the next 6 months had gradually increasing blood pressures, despite increasing dose quantities of antihypertensive medications. When last seen, 6 months after diazoxide therapy, his pressures were 270/130 reclining and 240/130 standing while taking guanethidine, 50 mg. to 500 mg., and reserpine, 0.2 or 0.5 mg. daily.

Patient 9 entered the hospital on no medication and received 16 diazoxide injections followed by 12 placebo injections. Chlorothiazide, 250 mg. daily, was started on the twelfth day of diazoxide therapy for the control of fluid and sodium balance and discontinued on the eleventh day of placebo injections. He was discharged on no medication, did well, and was readmitted to the hospital 1 month later for herniography which he underwent without difficulty. Thereafter he was followed in the Oakland Veterans Administration Hospital of Pittsburgh with increasing blood pressures necessitating increasing dosages of antihypertensive medications. When last seen 7½ months after diazoxide therapy he had a standing pressure of 180/130 while on alpha methyldopa, 2 Gm., and hydrochlorothiazide, 50 mg. daily.

Patient 10 entered the hospital on bethanidine, 20 mg. daily, and received 9 days of placebo injections, followed by 12 days of diazoxide. She had had a right nephrectomy for a shrunken, nonfunctioning kidney with a questionable renal artery lesion 1½ years previously with only temporary improvement in her hypertension. She received an average of 22 mg. of bethanidine daily while on placebo and 20 mg. daily while on diazoxide. Her entire hospital course was punctuated by deterioration of her cardiac status especially during the time of diazoxide injections. She required two 250 mg. doses of chloro-

Table II

Patient	*Period*			*Lying B.P.*			*Standing B.P.*			*Lying heart rate*			*Standing heart rate*	
	1	*2*	*3*	*1*		*3*	*1*	*2*	*3*	*1*	*2*	*3*	*1*	*2*
2 C. B.	C-4	D 11	—	175	148	—	139	125	—	73	99	—	90	105
3 G. S.	C-4	P 14	D 10	181	191	177	118	160	135	55	68	95	60	79
4 L. D.	C-4	I 16	D-3	119	111	95	114	108	96	74	88	74	80	95
5 V. M.	C-4	I 14	D-7	137	127	102	142	129	104	76	79	93	102	100
6 W. H.	C-4	D 14	P-0	159	130	—	126	127	—	74	91	—	79	95
7 M. I.	C-4	I 15	D-12	148	161	127	131	150	119	76	77	101	88	84
8, P. J.	C-4	D-14	P 14	140	121	148	98	120	147	53	70	64	66	89
9 G. D.	C-4	D-16	I 12	139	132	113	149	143	126	63	88	60	72	114
10 M. R.	C-4	I 9	D-12	144	163	136	135	153	117	74	82	86	70	81

Patient C. D. (No. 1, Table I) is not included in this table because of inadequate numbers of protocol blood pressures and pulse rates. [illegible]
Abbreviations: C = Control; D = diazoxide; P = placebo; H. Chlor. = hydrochlorothiazide; Chlor. = chlorothiazide; Guan. = guanethi[illegible]

thiazide during diazoxide therapy I addition, strict water and sodium restriction had to be imposed during the diazoxide period. After the end of diazoxide injections, bethanidine was discontinued and alpha methyldopa, 1 Gm. per day was started, along with ethacrynic acid, 100 mg twice weekly. She was readmitted to the hospital 4 weeks later with quite hypertensive pressures, Grade IV fundi, anasarca, and for the first time with renal failure. The methyldopa was discontinued and Inversine, 40 mg. daily was instituted with good control of her blood pressure. Diuresis as accomplished with fluid restriction and intermittent use of ethacrynic acid after which she was discharged from the hospital. Her blood pressure thereafter remained under fair control however progressive cardiac and renal failure necessitated two more hospitalizations and ere responsible for her death 5 months after diazoxide therapy

Results

The blood pressure responses to diazoxide are of two phases. The acute type is that which has been studied by others and is characterized by a marked hypotensive effect which reaches its nadir 1 to 3 minutes after injection. [4] In the next 5 to 10 minutes the mean arterial pressure rises from that low point to a new plateau which, although quite variable is consistently lower than the control values for that day In various patients this second phase was of variable duration lasting from 2 to 24 hours. The temporal characteristics of this second phase were prolonged enough so that 8 out of 10 patients required further reduction of their usual antihypertensive medication while receiving active drugs. The effects are summarized in Table II Mean reclining blood pressures for the final four days of diazoxide were significantly lower when compared to control ($p < 0.02$) Changes in mean standing blood pressure for the same period were not significant.

Pulse rate changes were also biphasic in character There was an immediate pulse rate increase in all patients upon injection.

During the initial days of active drug therapy this returned to control values within several hours. However as diazoxide injections were continued the return to control became delayed. This prolongation was present in both reclining and upright levels and indeed comparison of mean lying

Start of study		End of study		Cause for termination	Change in drugs required	
Date	Weight	Date	Weight		Initial drugs	Final drugs
12/8/66	62 1	12/19/66	65 3	Na & HOH retention	None	Died 2 days later
1/9/67	66 2	1/31/67	63 6	Lack of response, persistent vomiting	Beth., 15 mg.	Beth., 5 mg.
2/9/67	86 5	2/28/67	82 7	Normal B P hysterical reaction	Guan., 50 mg.	None
3/14/67	56 2	4/5/67	57 6	Disliked side effects and left study	Res., 0 1 mg	Res., 0.1 mg
3/16/67	61 5	3/29/67	61 7	Extreme vasospasm	Guan., 37.5 mg.	None
4 14/67	65	4/28/67	64	Completed study	Guan., 37.5 mg. H Chlor 100 mg.	H. Chlor 100 mg.
5 24/67	77 9	6/18/67	75 5	Completed study	Guan., 37.5 mg. Aldomet, 1.5 Gm. Res., 0.25 mg. Chlor 500 mg.	Chlor 500 mg.
6/25/67	105 9	7/22/67	101 6	Completed study	Guan., 50 mg.	Chlor 500 mg Beth 15 mg.
8 6/67	47 9	8/29/67	50 4	Na & HOH retention	None Beth., 15 mg.	Chlor 250 mg.

*Pressure and heart rates are means of last 24 hours in period
Res. = reserpine; Beth. = bethanidine; B.P. = blood pressure.

pulse rate for the last 3 days of diazoxide compared to placebo period showed a 33 per cent increase ($p < 0.01$) while a similar comparison of standing rates showed a 10 per cent increase ($p < 0.01$) This comparison contains a possible bias in that the amounts of therapeutic neuronal blocking agents (e.g bethanidine and guanethidine) were greater during placebo and control periods.

While there was the general impression of improvement of the eyeground findings in all patients with Grade III or IV changes evaluation of the eyeground photographs by independent observers did not change the actual grading of any sequence of photos

In addition one patient showed further progression of S-T and T wave changes on the electrocardiogram and 7 patients showed an increase in the number of premature ventricular contractions There were no significant differences between the control placebo and diazoxide periods in any of the laboratory values mentioned in the Methods section except for glucose tolerance changes mentioned below However 3 patients with previously compensated heart failure required additional thiazide diuretics during the period of diazoxide therapy Three additional patients required digitalization and/or thiazide diuretics for the first time for signs of congestive heart failure while on diazoxide A seventh patient required both digitalization and diuretics one week after the termination of diazoxide therapy

Subjective effects Immediate complaints of rapidly injected diazoxide were given by 9 out of 10 patients and included a peculiar taste in the mouth or throat a warm or rushing sensation in some part of their body (usually abdominal) abnormal odor and/or auditory phenomenon The patients were able to tell by the second injection whether they had received active drug or placebo These effects were short lived lasting up to 15 minutes. Four patients had pain along the vein being injected with diazoxide and in 2 of these associated venospasm necessitated the daily placement of an indwelling venous catheter None of these 4 patients were able to complete the study however 2 of them completed their course of diazoxide therapy one was discharged from the study after 11 injections at the decision of his physicians and the fourth left the study of her own volition after 7 diazoxide injections. Subcutaneous infiltration of part of the bolus on 6 occasions in 3 patients occurred resulting in a severe burning sensation however there was no tissue sloughing

During the course of the study we observed that most of the patients complained of either abdominal or low back discomfort. They described a vague discomfort that was exaggerated by standing Most of the patients also complained of the development of constipation Prompted by these complaints, two additional procedures were added to the protocol for the last 5 patients studied (1) Bowel sounds were listened for before and after injection of diazoxide. (2) Serum amylase levels were obtained during control and active drug injection periods In these 5 patients, 4 consistently had normal bowel sounds before injection and hypoactive to absent bowel sounds for approximately 20 minutes after injection. Three of these 5 patients had elevation of serum amylase levels while on diazoxide therapy One of these later patients did not have a change in bowel sounds so the relationship between the two findings is not clear

Other subjective effects noted included restlessness sleeplessness and increased irritability but frequency of these complaints did not differ from that observed during placebo therapy

Metabolic changes One patient was a known diabetic and eight of the remaining nine had abnormal glucose tolerance curves during control period Seven of these nine had an increase of their fasting blood sugar levels when diazoxide period was compared with control The one patient with originally normal glucose tolerance developed a diabetic glucose tolerance curve while receiving diazoxide Fasting blood sugar elevations were mild in all but Patient No 2 in whom they ranged between 101 and 149 mg per 100 ml Patient No 2 after 11 days of diazoxide therapy had an elevation of his fasting blood sugar to 615 mg per 100 ml. Twenty units of regular insulin brought the level back to a normal range.

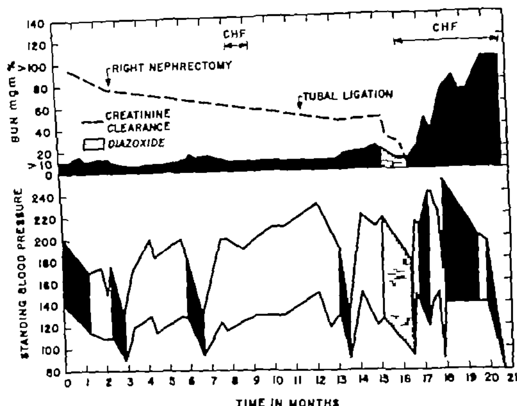


Fig. 2. Clinical course of Patient 10 before and after receiving diazoxide until her death 5 months later. Black areas represent periods of hospitalization. The speckled area represents the period of hospitalization during which she received diazoxide for 12 days.

Long-term effects. At the time of this report 9 months after the conclusion of the study, half of the patients studied are dead. No significant consistent change was seen in the duration of the antihypertensive response after cessation of treatment in any of the survivors. Nor was there any evidence that diazoxide injections resulted in making these patients more sensitive to previously ineffective medication. Fig. 2 illustrates the progression of the hypertensive process in Patient No. 10, one of the patients who died of progressive renal and cardiac failure, in spite of temporary improvement while receiving diazoxide. Note the almost identical drop in blood pressure during the first five admissions, including the diazoxide hospitalization and the equally similar return to prehospitalization blood pressures. Despite good control of the blood pressure and blood urea nitrogen while on diazoxide, the creatinine clearance continued to fall prior to the onset of intractable congestive heart failure, renal failure, and death. The other 4 patients who died also had numerous pre- and/or postdiazoxide therapy hospitalizations for accelerated hypertension and their graphic histories are quite similar to that shown in Fig. 2. Of the 5 patients who are still alive (Patients 4, 5, 7, 8, and 9) a similar common course was seen with each patient's blood pressure returning to prestudy levels in spite of increasing dosages of oral antihypertensive medication (at 3, 9, ½, 4, and 2½ months, respectively). Furthermore, there seemed to be continued progression of the disease as manifested by funduscopic, cardiac, and renal changes. Previous hospitalization in 3 patients (Nos. 7 and 9) suggested no characteristics of blood pressure control that indicated a persistent effect of the diazoxide therapy. Fig. 1 demonstrates one such patient living and still under observation (No. 7). If one compares Fig. 1 to the diazoxide and pre

diazoxide portion of Fig. 2 they appear quite similar. We have been unable to predict from the blood pressure, cardiac status, or response to diazoxide which patients would live or die in the study group.

Postmortem results. Postmortem examinations were obtained on all patients who died (Patients 1, 2, 3, 6, and 10). No changes attributable to diazoxide therapy were seen.

Discussion

The data from these studies are quite consistent with that from other laboratories in demonstrating the efficacy of intravenously administered diazoxide in rapidly reducing arterial pressure.[1,3] There was a significant drop in blood pressure at the end of the diazoxide period suggesting some persistence of the hypotensive effect.

The beneficial effects of repeated diazoxide injections (lower pressures and slower progression of the consequences of hypertension) were of much shorter duration in our patients than in others reported in the literature.[1,4] We are at a loss to explain this except to suggest a difference in patient population and selection.

A distinct disadvantage of this form of therapy is the finding of fluid retention and the appearance of cardiac failure. Six of the patients showed measurable sodium retention while receiving diazoxide. The other patients were maintained on digitalis and/or thiazide preparations (other than diazoxide) until their diazoxide therapy was completed, thus confounding potential sodium and weight differences present in the drug period. The fact that diazoxide is non-saluretic is well known.[4,5] The increased sodium and fluid retention seen in our patients may be in part due to the fact that our patients received more intravenous diazoxide over a shorter duration than patients in other studies.[1] In addition, the recent work of Naylor and associates[6] shows that ventricular function curves were displaced to the right with diazoxide in dogs, indicating a diminution in the capacity of the left ventricle for doing external work. Insofar as this finding is applicable to humans, it suggests that diazoxide could unmask or exaggerate congestive heart failure. This would explain why the cardiac status of our patients failed to improve while on diazoxide therapy in spite of increased bed rest and lowered blood pressure.

These findings suggest that diazoxide therapy is no more effective than conventional antihypertensive agents. The authors are quite aware that the unequal duration of control and placebo periods, the poor randomization of patients into therapeutic groups, the effects of alteration of other medication while on the drug under study, and the variable periods that patients were on active drug are all factors which detract from the intended purity of this study. However, they demonstrate the difficulties in doing a definitive study in seriously ill hypertensive patients with a drug which has, at best, equal efficacy, equally numerous and serious side effects, and the added disadvantages inherent in intravenous administration (when compared to conventional oral antihypertensive agents). The patients clearly preferred their oral medication and complained frequently of the abdominal discomfort, constipation, and restlessness as well as the bother of daily injections.

While the lack of significant change in the majority of laboratory examinations suggests that this is not a more toxic form of therapy, the data do not demonstrate significant efficacy. The failure of this therapeutic approach may be due as much to a faulty hypothesis regarding the amelioration of hypertension as it is to failure of a specific medication. We doubt the hypothesis that a short period of normo- or near normotension will reverse the underlying arterial lesion, reset the barostat,[1] or affect the other factors which present as essential hypertension, no matter what drug is used.

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Atrial fibrillation associated with acute myocardial infarction A study of 34 cases

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The advent of continuous electrocardiographic monitoring systems and coronary care units has made it possible to observe closely and evaluate the electrocardiogram (ECG) changes associated with acute myocardial infarctions These innovations were originally used to evaluate life-threatening ventricular arrhythmias but with the added interest in newer cardiac drugs cardiac pacemakers and cardioversion they have been extensively used to study the less serious arrhythmias which often develop into major arrhythmias or else can cause hemodynamic abnormalities. Excluding premature beats atrial fibrillation has been found to be a common postinfarction arrhythmia It has been the subject of many studies both before and after the institution of coronary care units.

Most studies have been concerned primarily with the incidence of atrial fibrillation and the mortality it produces. We have evaluated the characteristics of myocardial infarction-induced atrial fibrillation with regard to incidence, mortality rate previous cardiovascular disease location of infarction mode of onset and duration of the arrhythmia effects of medications, and associated complications. The prognostic significance of atrial fibrillation is also discussed

Procedure and materials

There were 31 patients with atrial fibrillation among the 409 patients admitted to the Los Angeles County–University of Southern California Medical Center Coronary Care Unit between 1966 and August 1968 They were predominantly from the lower socioeconomic population in the Los Angeles area and their admission to the unit and study program was on a bed available basis. The study involved 19 men and 12 women of which 4 were Negro and 27 were Caucasian Their average age was 66 1 years with the range being from 48 to 85 years.

The myocardial infarction was confirmed on the basis of a characteristic history ECG changes, and elevated white blood count erythrocyte sedimentation rate and the enzymes serum glutamic oxalacetic transaminase (SGOT) and creatine phos-

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phokinase (CPK). Congestive heart failure was diagnosed on the basis of x-ray findings (cardiomegaly, differential blood flow to the upper lobes, vascular congestion, and Kerly's lines), distended neck veins, hepatomegaly, persistent râles, gallop rhythm, or increased central venous pressure. Shock was evident when there was a systolic blood pressure less than 80 mm Hg, decreased or absent peripheral pulses, cold and clammy extremities, cyanosis, and oliguria.

On admission a 12 lead ECG was taken and the patients were then attached to an oscilloscope which was monitored by a cardiac nurse. The patients were kept at strict bed rest with a low-salt diet, oxygen, sedation, and diuretics as required. The patients were observed for a minimum of five days after admission and longer in those cases in which the patient's condition was unstable.

Clinical findings

Incidence. We found 31 cases of atrial fibrillation associated with 409 cases of acute myocardial infarction (7.5 per cent). This value does not include 3 cases of atrial fibrillation in which the arrhythmia was known to be present before the infarction. Table I depicts the incidence and mortality rates found in other studies both before and after continuous monitoring systems were developed. In the premonitoring period before 1964, the incidence of atrial fibrillation associated with myocardial infarction was 7 per cent (343 instances among 4,968 cases) while the incidence in the continuously monitored studies was 9 per cent (125 instances among 1,372 cases). Though the advent of continuous monitoring systems was expected to demonstrate an increased incidence of atrial fibrillation, this has not been the case and can be explained by several con

Table I

Study	Incidence			Mortality		
	Cases	Atrial fib.	% Atrial fib.	All MI (%)	Atrial fib. (%)	Increased mortality
Premonitoring						
Levine (1929)	145	34	23	32	53	N
Howard (1934)	165	10	6	24	70	Yes
Master (1937)	300	22	7	22†	45	Yes
Askey (1945)	1,247	84	8	51	38	No
Chambers (1946)	100	10	10	34	60	Yes
Mintz (1947)						
Rosenbaum (1941, 1947)	208	25	12	32	36	No
Bellinger (1949)	240	—	11	40	65	Yes
Smith (1951)	920	44	5	23	32	Yes
Binder (1955)	300	20	7	42*	65	Yes
Johnson (1958)	187	16	9	23	31	N
Beard (1960)	503	29	6	15	28	Yes
Imperial (1960)	153	15	10	40	74	Yes
Hurwitz (1964)	500	34	7	27	38	Yes
Monitored						
Julian (1964)	100	16	16	31	16	N
Meltzer (1966)	141	—	7	—	—	—
Fluck (1967)	50	7	14	24	14	No
Stock (1967)	200	15	7.3	30	33	No
Jewitt (1967)	222	24	11	24	29	N
Stannard (1967)	250	22	9	28	41	Yes
Klass (1969)	409	31	7.6	15	42	Yes

*Mortality for infarcts associated with other arrhythmias.
†Mortality for infarcts not associated with other arrhythmias.

Table II Atrial fibrillation cases

Case history	All (%)	Lived (%)	Died (%)	χ^2	Signif
Previous infarction	42	33	54	1 61	NS
Previous angina	65	44	92	5 00	$p<0.05$
Previous hypertension	45	28	69	5 20	$p<0.05$
Previous CHF	39	44	31	0 75	NS
Previous diabetes	39	33	46	0 75	NS
Total previous disease	81	72	92	0 72	NS
Anterior infarction	61	50	77	2 16	NS
Associated CHF	81	72	92	0 72	NS
Associated shock	35	22	54	7 26	$p<0.01$
Ventricular rate (>120)	45	39	54	0 93	NS
SGOT (> 200)	45	33	62	2 93	NS
Age	66 1	67 8	63 7		
Persistence (>3 days)	3 cases	1 case	2 cases		
Onset (after day 2)	4 cases	1 case	3 cases		

CHF = Congestive heart failure

siderations First because of its irregularity and pulse deficit atrial fibrillation has been easily diagnosed without the aid of a rhythm strip Second the early onset of atrial fibrillation after a myocardial infarction made it easy to pick up on admission ECG s and during the first day when vital signs were frequently taken Third some studies just examined short samples of the daily tracings and undoubtedly missed some of the short bursts of atrial fibrillation which are known to occur Others only monitored the patients for a few days while still others used alarms which started the tracings when there was a marked change in ventricular rate which doesn t always occur in controlled atrial fibrillation Finally some patients may have had atrial fibrillation and died before reaching a monitoring station Thus, it is likely that there is actually a higher incidence of atrial fibrillation than is recognized but this cannot be substantiated by available information

Mortality rate We found that 13 of the 31 patients (42 per cent) with atrial fibrillation died while the average mortality rate for all myocardial infarction patients during the same period was 15 5 per cent Previous studies shown in Table I have had an average mortality rate for atrial fibrillation associated with myocardial infarction of 37 per cent with extremes of 14 per cent[8] and 74 per cent[12] Askey and Neurath[1] emphasized that the mortality rate for persistent (greater than one day) atrial fibrillation (80 per cent) was greater than that for the transient arrhythmia (58 per cent) and we found similar results with 39 per cent of the transient and 67 per cent of the patients with persistent atrial fibrillation expiring Almost half of the previous studies demonstrated that the mortality rate associated with atrial fibrillation was higher than the mortality rate for all infarction patients[1-4,10,12,16,22,24] while Askey s study indicated that the mortality rate was higher only for the persistent group of fibrillators. Our study indicated an increased mortality rate over the general group but whether there is a direct cause-effect relationship will be discussed later

Previous cardiovascular disease There were 13 patients among the 31 (42 per cent) who had previous myocardial infarctions. This same incidence occurred in all of the patients followed in the coronary care unit Master and associates[20] also found that patients with atrial fibrillation did not have an increased incidence of previous infarctions. We did find however that only 33 per cent of those that lived had previous infarctions while 54 per cent of those that died had previous infarctions. Of the three cases with two or more previous infarctions two died

Sixty five per cent of the patients had

a previous history of angina averaging four years in duration. This is compatible with the 72 per cent found by Rosenbaum and Levine.[14] However 9 per cent of those that died had a previous history of chest pain which averaged 6.2 years in duration while only 44 per cent of those that lived had similar pre-existing symptoms averaging 2.4 years.

Pre-existing hypertension also affected the mortality rate with 69 per cent of those dying being affected while only 28 per cent of those living had the same condition. It is however difficult to evaluate the pre-existence of hypertension since many patients had not been seen by a doctor for many years prior to the infarction. Master's study[29] for example found a previous history of hypertension in 86 per cent of his study while we only found a 45 per cent incidence.

The presence of pre-existing diabetes and congestive heart failure did not seem to alter the prognosis.

Thus, with all of these factors combined 81 per cent of the 31 patients had some previous cardiovascular disease and as many as 92 per cent of those that died were affected.

Age. The average age of the patients in this study was 66.1 years. This is about six years older than the average age found in other studies[1, 4,23,24] and is probably due to the difference in populations. Interestingly, the average age of those patients who died was four years younger than those who survived.

Location of infarction. There were 16 cases of atrial fibrillation involving the anterior wall and 13 involving the posterior wall. There was no difference in the mortality rates in relation to location although one of the two patients with both walls affected died. Other studies[1,4, 11,12, 18,22,24,25] have also demonstrated an equal distribution between anterior and posterior infarcts associated with atrial fibrillation and Chambers[4] also noted the increased mortality rate in those cases involving both walls. Jewitt and associates,[14] on the other hand found that three times as many cases involved the anterior wall.

Date of onset. The time of onset of atrial fibrillation in relationship to onset of infarction is difficult to assess because it is difficult to determine exactly when the infarction occurs. When both occur before the patient reaches the hospital it is difficult to determine whether the atrial fibrillation may have been present before the infarction. We found that in 16 of the 31 cases auricular fibrillation was either present on admission or began within 24 hours of the estimated time of infarct and 27 of 31 cases (87 per cent) within 48 hours. The 4 other cases occurred on postinfarction days 3, 4, 5, and 8. The transitory nature as well as the rapid responses on admission suggested that previously undiagnosed chronic atrial fibrillation was unlikely.

Other studies[24,25,26] have reported only 30 to 60 per cent of the fibrillation occurring before the third postinfarction day and also reported the arrhythmia occurring as late as the third to fifth week. Whether these "late onset" cases were directly induced by the infarction or by some other causes (i.e. shock, congestive heart failure) is questionable. We found that there was no correlation between the time of onset of the atrial fibrillation and the prognosis except in the 4 "delayed onset" cases in which 3 died. These cases, however, were each complicated by either shock, severe congestive heart failure, renal cortical necrosis, or ventricular tachycardia and the fibrillation may have only been secondary to these insults. Thus, late onset fibrillation is associated with a poor clinical course and prognosis.

Mechanism of onset. The mechanism of onset of the atrial fibrillation was documented in 18 of the 31 cases and half developed following a premature atrial contraction while the other half resulted from a transition from atrial flutter. Killip and Gault had similar findings but most of their cases (78 per cent) followed premature atrial contractions. Imperial and coworkers[17] reported 4 cases following a normal sinus beat. (Atrial flutter frequently begins by a similar mechanism and our experience with these cases is being separately analyzed.)

Ventricular rate. The average ventricular response of the atrial fibrillation in this study was 102 beats per minute with almost

half (45 per cent) being greater than 120 beats per minute Of those that survived only 39 per cent had rates greater than 120 Other studies[20] have also reported an increased mortality rate with an uncontrolled ventricular response while still others[16] have not verified this finding and have even indicated that a slower rate may be more harmful

Duration We found that 22 of the 31 cases (71 per cent) lasted less than four hours and 28 of the 31 cases (90 per cent) lasted less than 24 hours. Some episodes lasted only several seconds, but these usually recurred Most other studies[6,9,14,16,20,21,24] agree that 80 to 90 per cent of all episodes of atrial fibrillation last less than 24 hours and usually last less than 4 to 6 hours. These transient cases are usually associated with a low mortality rate The 3 persistent cases comprised 10 per cent of the study cases and 2 of the 3 died Interestingly enough 2 of the 3 cases of systemic emboli occurred in the persistent atrial fibrillation cases. One died with a pulmonary embolus while the second survived after a right femoral embolectomy The third patient died in shock but no emboli were found Some studies[20,21,24] report only 0 to 8 per cent incidence of persistent atrial fibrillation following an infarction while others[1,4] have reported as many as 60 to 65 per cent The latter studies, however used lesser criteria in calling a case persistent All of these studies however agreed with our findings that the persistent arrhythmia is associated with a higher incidence of mortality Askey and Neurath[3] also corroborated our findings that the persistent variety of atrial fibrillation is associated with concurrent cardiovascular complications and that the likelihood of embolization is increased

Recurrence The recurrence of atrial fibrillation after the first episode was found to be significant in relation to when the second episode occurred but not related to the number of recurrences. Seven patients (23 per cent) developed a second episode of atrial fibrillation more than one day after the first episode Table III shows that there were no deaths in those cases in which atrial fibrillation recurred in less than 4 days after the initial attack but that there was a 100 per cent mortality rate in those recurring after this period We must note however that the high mortality group also had more complications (especially other arrhythmias) and thus the fibrillation may have been the effect rather than the cause of the downhill course

SGOT The SGOT values were useful as a prognostic sign in myocardial infarctions as a whole and not particularly related to the atrial fibrillation The average SGOT value for the 31 patients was 201 but nearly two thirds (62 per cent) of the patients that died had SGOT values greater than this (average 263) while one third of those that lived had values greater than 201 These differences are probably not statistically significant because of overlap In actuality however the more specific enzymes (i e CPK) would seem to be better prognosticators since congestive heart failure secondary to the infarction may also raise the SGOT and give a falsely elevated value There were for example two cases in which the patient developed congestive heart failure with SGOT values of near 3 500 and only one of the two patients died

Associated complications Thirty five per cent of the patients with atrial fibrillation developed shock as defined in the protocol This compares with 54 per cent found by Rosenbaum and Levine[24] in all of their infarction cases. Only 22 per cent of our surviving patients developed clinical shock while 54 per cent of those that died were in shock at some time during their illness.

The most commonly associated complication of atrial fibrillation associated with myocardial infarction was congestive heart

Table III

Days between 1st and 2nd episodes of fibrillation	2	2	3	4	5	11	20
Result	S	S	S	S	D	D	D

S = Survived; D = died.

failure with 81 per cent of the patients being affected. Master and associates[20] and Julian and co-workers[14] found similar values of 81 and 75 per cent, respectively. We observed a higher incidence of failure in those patients that died (92 per cent) as compared to those that survived (72 per cent). Although it is known that atrial fibrillation compromises cardiac output and potentiates congestive heart failure, the reverse may also be true in regard to infarctions. Luten and Jeffries[11] and Nahum and Hoff[22] postulated that the damaged heart produces ventricular insufficiency which in turn increases auricular pressure, dilates and stretches the muscle fibers, and thus may induce atrial fibrillation. Thus the fibrillation is secondary to the failure and not its cause. They also postulated that there must be an accompanying vagal influence, autonomic reflex, or as yet unknown factor involved since our study and others[29] have noted that atrial fibrillation may occur either before, during, or after the episode of congestive heart failure has subsided and that atrial fibrillation does not occur in all cases in which congestive heart failure is present. It is, however, important to recognize this association so that congestive heart failure may be detected early.

The association of other arrhythmias was too varied to adequately evaluate.

Embolization. There were three patients (10 per cent) among the 31 who had clinical evidence of embolization and two of the three died and embolization was verified at autopsy. All three had not previously been on anticoagulants. Other studies[14, 4] have found similar incidences of embolization while Stannard and Sloman[28] reported no emboli among his 22 patients who were on anticoagulants. These studies did not indicate that atrial fibrillation alone increased the hazard of embolization following an infarction. Askey and Neurath, however, found that 6.8 per cent of all infarction patients have emboli and that atrial fibrillation definitely increased this risk regardless of other factors. They also found that congestive heart failure associated with atrial fibrillation almost doubles the incidence of embolization. Actual figures are difficult to evaluate because there may be many instances of small emboli which are not clinically evident and which never reach the autopsy table. Second, many episodes of fibrillation are very transient and are less likely to produce emboli than are long-standing cases as were observed in Askey's paper. Third, all of our cases were also associated with other arrhythmias, and these may also produce emboli (i.e., ventricular fibrillation). It is also difficult to determine whether the emboli occurred before, during, or much later than the episode of atrial fibrillation, and this makes the correlation even more difficult.

Therapy. The exact place of digitalis, quinidine, and procainamide in the treatment of atrial fibrillation associated with myocardial infarction has been debated for many years. Some studies[11, 20, 22, 28, 29] have demonstrated either no benefit or an increased mortality with the use of these cardiac drugs. Luten and Jeffries even felt that digitalis may prolong the arrhythmia. Others have indicated that cardiac drugs may be beneficial in either slowing the ventricular response or converting the irregular rhythm to a sinus mechanism but only under certain conditions. Some studies[7, 13] suggest that digitalis should only be given if the fibrillation is persistent or if the patient is symptomatic. Others[29] indicate that no digitalis should be given during the first postinfarction week because of the presence of cardiac muscle irritability and the deleterious effect of increasing myocardial contraction in an already weakened heart. (Digitalis could then be started during the second week when the danger of myocardial rupture and embolization had passed.) Our

Table IV

Therapy	*Survived*	*Died*
No therapy	1	1
Digitalis alone	1	3
Pronestyl or quinidine alone	2	0
Digitalis and Pronestyl or quinidine	14	9
Anticoagulants	8	8
Electrical cardioversion	2	0

study did not demonstrate any adverse effects from judicious use of these drugs although only two of our patients received no medication (Table IV)

The more severely ill patients received both digitalis and procainamide or quinidine and their mortality rate was only 39 per cent Although it is difficult to evaluate the extent to which the digitalis actually produced other arrhythmias it was felt that the improvement in congestive heart failure myocardial perfusion and slowing of the ventricular response greatly outweighed any disadvantages of its use The increased risk of perforation was not recognized since there was only one case of myocardial perforation and that patient was not on any cardiac drug

We attempted to evaluate the effectiveness of digitalis and quinidine like drugs in either the conversion or prevention of recurrence of atrial fibrillation The transitory nature of the arrhythmia in most of the patients and recurrence despite drug therapy in others led us to conclude that neither digitalis nor quinidine like drugs was definitely prophylactic or induced reversion regularly On the other hand control of ventricular rate could be effected with digitalis

Electrical cardioversion has been reported to be effective[14] to convert atrial fibrillation to normal sinus rhythm after infarction However because of its transitory nature we feel that this technique is not often indicated except when acute cardiovascular collapse is imminent We attempted two successful DC cardioversions in patients with sustained atrial fibrillation

Half of our patients were anticoagulated because of either persistent fibrillation or suspicion of embolization The over all mortality rate was equal in the anticoagulated and nonanticoagulated groups. However three cases of clinical embolization occurred in the nonanticoagulated group and none in the anticoagulated group suggesting a prophylactic role of anticoagulants in patients with persistent atrial fibrillation

Pre-existing atrial fibrillation There were three cases in which pre-existing atrial fibrillation was documented and these cases were considered separately because they did not begin as a direct result of the infarction All three of these patients had previous anterior myocardial infarcts (Table III) subsequent angina and were on digitalis at the time of the second infarct. One patient had a ventricular rate of 80 and did not develop any complications although his arrhythmia persisted. The second also had a ventricular rate of 80 but had associated diabetes with hypertension and developed congestive heart failure and shock The autopsy revealed a renal artery embolus. The third patient had a poorly controlled ventricular response (130) and associated congestive heart failure He also died but no emboli were found at autopsy

Prognosis This study indicated that atrial fibrillation is in itself a benign complication of a myocardial infarction and that its prognostic significance relates to the severity of the complications such as congestive heart failure shock hypertension and associated arrhythmias Other studies[3,4,18,20,27] have had similar conclusions We also felt however that a previous history of an infarct or angina infarcts involving both the anterior and posterior myocardial walls and SGOT values above 200 carried a poorer prognosis A careful analysis of the characteristics of the fibrillation indicated that when the arrhythmia occurred for the first time after the third postinfarction day persisted recurred later than 4 days after the first episode or had a rapid ventricular rate the prognosis was worse and usually indicated coexisting complications Smith and co-workers[23] on the other hand did not feel that pre-existing hypertension or angina increased the mortality rate and Stannard and Sloman[14] did not feel that it was related to the time of onset or duration of the arrhythmia In our study we did not find any correlation between the prognosis and pre-existing congestive heart failure diabetes or the location of the infarct providing it only involved one wall Thus it is felt that atrial fibrillation is primarily an effect rather than a cause of complications following a myocardial infarction and that it should make one aware of coexisting complications. We have how

ever indicated some characteristics of the arrhythmia itself which do help indicate what the eventual outcome will be regardless of the etiology. Table II indicates those factors that despite the small numbers, have statistical significance.

Conclusions

1. The *incidence of* atrial fibrillation following a myocardial infarction is 7 6 per cent and has not increased with the advent of continuous monitoring systems.

2. There is an increased mortality rate (42 per cent) for infarction patients with associated atrial fibrillation but this is primarily a result of concurrent complications and not the arrhythmia itself.

3. Most episodes of atrial fibrillation begin within the first 48 hours (87 per cent).

4. Half of the cases start with a premature atrial contraction while the other half evolve from atrial flutter.

5. The duration of the fibrillation is short with 74 per cent lasting less than 4 hours and 90 per cent lasting less than 24 hours.

6. Atrial fibrillation was not shown to cause an increased incidence of embolization unless it persisted.

7. There was no contraindication to using cardiac drugs while DC shock was found to be an effective and safe means of cardioversion.

8. Anticoagulants may have decreased the incidence of clinical embolization but not the mortality.

9. A poor prognosis was indicated by a previous history of infarction, angina or hypertension infarction of both myocardial walls associated shock congestive heart failure or other arrhythmias high SGOT values (greater than 200) rapid ventricular response late onset (after the third day) persistence of the arrhythmia recurrence of the fibrillation more than 4 days after the first episode.

10. There was no relation between the mortality rate and pre-existing diabetes congestive heart failure or the location of the infarct providing it only involved one wall.

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Hospital registration in patients with acute myocardial infarction

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In the last six years, a considerable amount of information has accumulated from the study of patients with acute myocardial infarction in coronary care units. This information has been well reviewed in a Rand Corporation Publication (Rockwell[9]) At the present time, there is very little known about the outcome of all patients presenting at a hospital with a provisional diagnosis of a "heart attack." Some information has been provided in a retrospective study by Cross, however prospective information would be more valuable in viewing the problem in perspective.

We here present a review of all patients admitted to the Royal Melbourne Hospital during a six-month period with a provisional diagnosis of acute myocardial infarction as well as those patients who, while in hospital were shown to have a recent myocardial infarction.

Methods and materials

Since March 1 1968 *a register has been* kept of all patients admitted to the Royal Melbourne Hospital with a provisional diagnosis of acute myocardial infarction. In order to obtain a near complete cover of all patients, the hospital and autopsy records were also searched electrocardiograms were reviewed and a personal liaison was *established with the medical wards in an* attempt to obtain complete registration of all patients with definite or suspect acute myocardial infarction.

Each registered patient was seen by one of us and a special pro forma designed for the study was completed. The reviewer took no part in the management of the patients but saw the patients on two or three occasions during the hospital stay to confirm the clinical observations and to *obtain standardization in the reports on chest* x rays and electrocardiograms (ECG's) The Minnesota Code[11] was used for reporting the ECG's. Electrocardiograms with Q and Q-S changes coded as 1 1 1.2 1.3 together with sequential S-T and T-wave changes (9-2) were recorded as having unequivocal electrocardiographic evidence of infarction T wave changes alone (5-1 to 5-4) were regarded as equivocal electrocardiographic evidence of acute myocardial infarction Enzyme levels of serum glutamic oxalacetic transaminase greater than

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40 units serum lactic dehydrogenase greater than 250 units and creatine phosphokinase activity levels greater than 70 units were regarded as positive levels

By considering the history ECG and enzyme studies the patients were classified into one of the following six diagnostic groups according to World Health Organization classification

Class 1 Definite acute myocardial infarction This group includes patients with (a) unequivocal ECG evidence of recent infarction (sequential changes of injury current or the observed development of abnormal Q waves) with or without a typical history (b) equivocal ECG evidence of recent infarction with abnormally high level(s) of the appropriate serum enzyme(s) with or without a typical history (c) normal ECG with abnormally high level(s) of appropriate serum enzyme(s) and a typical history (d) postmortem evidence of acute myocardial infarction

Class 2 Probable acute myocardial infarction This group comprises cases with a typical history but with equivocal ECG evidence of recent infarction and equivocal elevation of serum enzyme level(s)

Class 3 Possible acute myocardial infarction This class comprises cases with a typical history but either equivocal or no ECG changes of infarction and with no elevation of serum enzyme level(s)

Class 4 Atypical cases The patients in this class have histories which were atypical and there were no significant abnormalities of the ECG or serum enzyme level(s)

Class 5 No acute myocardial infarction In this class, another definite diagnosis was made

Class 6 Insufficient data This group comprises cases with insufficient items of evidence to allocate to the categories 1 2 3 or 4 but where no other diagnosis was positively made.

No attempt was made to classify the infarction on the basis of severity but the following clinical features noted on admission were recorded Pulse rate and rhythm blood pressure presence of peripheral vasoconstriction cyanosis, degree of consciousness, cardiac enlargement added heart sounds pulmonary crepitations elevation of systemic venous pressure edema pericardial friction rub and/or cardiac bruits. Cardiogenic shock was diagnosed when the systolic blood pressure was below 90 mm Hg and there was evidence of shock as manifest by peripheral vasoconstriction and oliguria.

The coronary care unit at the hospital consisted of a two-bed ward with ECG monitoring and continuous nursing observation Patients were admitted to the unit on a bed available basis or referred because of some severe complication of myocardial infarction

Results

In the six months under review 278 patients were registered Of these 79 (28 4 per cent) were treated in the coronary care unit. The over-all incidence sex and mortality rate in each World Health Organization class is shown in Table I Of the total of 278 patients 96 (34 5 per cent) were females and 182 were male but females constituted only 17 7 per cent of the coronary care unit groups.

The 222 patients (80 per cent of the groups) who were classified into Class 1 (definite acute myocardial infarction) had a hospital mortality rate of 24 3 per cent There were 6 18 12 10 and 10 patients in Classes 2 to 6 respectively

The 10 patients admitted with a provisional diagnosis of acute myocardial infarction who were later found to have another definite diagnosis (Class 5) had the following conditions pulmonary embolism cholelithiasis abdominal pain with epilepsy thyrotoxic cardiomyopathy chest infection pericarditis and acute pulmonary edema without identified cause and two had influenza The only death in this group occurred in the remaining patient a woman with a dissecting aortic aneurysm The ten patients in Class 6 were all admitted moribund and died soon after No clinical diagnosis was made investigations were not begun and autopsy was not performed in any case It was considered that the majority of these had nevertheless suffered an acute myocardial infarction however this could not be confirmed

The incidence and mortality of the 258 patients in Classes 1 to 4 as related to age are shown in Table II The mean age of all

Table I Sex incidence and mortality rate of each of the W.H.O groups

Hospital or C C U	Class 1 (Definite)	Class (Probable)	Class 3 (Possible)	Class 4 (Atypical)	Class 5 (Y A M I)	Class 6 (Insufficient data)	Total
Hospital							
Males	90	3	13	4	3	4	117
Females	60	2	4	7	4	5	82
(Mortality rate)							(41.2%)
Total	150	5	17	11	7	9	199
Deaths	37	1	6	0	0	9	33
(Mortality rat)	(24 6%)	(20%)	(35%)	(0%)	(0%)	(100%)	(26.5%)
C C U							
Males	59	1	1	1	2	1	65
Females	13	0	0	0	1	0	14
(Mortality rate)							(17 7%)
Total	72	1	1	1	3	1	79
Deaths	17	0	1	0	1	1	20
(Mortality rate)	(23 6%)	(0%)	(100%)	(0%)	(33%)	(100%)	(25.3%)
Total (Hospital and C C U)							
Males	149	4	14	5	5	5	182
(Mortality rate)							(65.5%)
Females	73	2	4	7	5	5	96
(Mortality rate							(34.5%)
Total	222	6	18	12	10	10	278
Deaths	54	1	7	0	1	10	73
(Mortality rate)	(24 3%)	(16 6%)	(39%)	(0%)	(10%)	(100%)	(26.3%)

C C U coronary care unit

Table II Patients in Classes 1 to 4 grouped by age and area in which treated

Hospital or C C U	30-39 y	40 49 yr	50-59 y	60-69 yr	70-79	80-89 yr	Total
Hospital group							
Total	3	23	39	62	47	9	183
Deaths	0	0	4	19	20	1	44
Mortality ra ( )	0	0	10 3	30 6	42.5	11 1	24
C U group							
Total	3	15	26	27	4	0	75
Deaths	2	1	4	10	1	0	18
Mortality rate ( )	66	6 6	15 4	37	25	0	24
Total (Hospital and C C U)	6	38	65	89	51	9	258
Deaths	2	1	8	29	21	1	62
Mortality rate (%)	33	2 6	12.3	32 6	41	11 1	24
Per cent of total no of patients	2	14	25	37	19	3	100
Per cent of group in C C U	50	39 4	40	30	8	0	29

C.C Coronary care unit

patients in Classes 1 to 4 was 61 1 years while that of the 75 patients admitted to the coronary care unit was 56 2 years Table II shows that a greater proportion of the younger patients was treated in the coronary care unit. If we exclude the first and last age grouping where the numbers are small it can be seen that there is a rising mortality rate with age from a low of 2 6 per cent in the 40 to 49 age groups to a high of 41 per cent in the 70 to 79 age groups. The highest mortality rate in the coronary care unit patients (37 per cent) was in the age group 60 to 69 years, while the hospital ward patients registered their highest in the next older decade (42 5 per cent)

Table III compares the sex incidence and the age. Although female patients constituted roughly one third of the total they made up a greater proportion of the older age groups 70 to 79 years and 80 to 89 years. Their hospital mortality rate 33.3 per cent was higher than the mortality rate of the male groups (19 3 per cent) If one looks at the mortality under and over 60 years of age we find 6 of 29 females under the age of 60 dying (20 per cent) while 5 of 80 males died (6 0 per cent) The male mortality is noticeably different ($p > 0.1$) Over 60 years, 28 of 91 males died (31 per cent) while 23 of 58 females died (40 per cent) In this situation there was no statistical difference between the two groups ($p > 0.70$)

The period between the onset of infarction and the time of admission to hospital is shown in Table IV (Three per cent of the infarctions occurred in hospital and the majority of these were associated with acute surgical blood loss.) Ninety-eight patients (38 per cent) were admitted to hospital

Table III *Age of registration related to sex and hospital mortality rate*

Age groups	*30 39*	*40-49*	*50-59*	*60-69*	*70-79*	*80-89*	*Total*	*Mortality rate (%)*
Females	1	7	21	26	25	7	87	33.3
Males	5	31	44	63	26	2	171	19.3
Per cent of group being female	17	18	32	29	50	78	33 7%	
Deaths Female (Mortality rate)	0	0	6 (28.5%)	11 (42.3%)	12 (48%)	0	33.3%	
Deaths Male (Mortality rate)	2 (40%)	1 (32%)	2 (45%)	18 (28.5%)	9 (35%)	1 (50%)	19.3%	

Table IV *Outcome in patients admitted within six hours of the onset of severe pain (Classes 1-4)*

Hospital or C C U	*0-1 hr*	*1 2 hr*	*2 3 hr*	*3-4 hr*	*4-5 hr*	*5-6 hr*	*Total*
Hospital	3	3	9	17	10	17	59 (60%)
Deaths (Mortality rate)	0 (0%)	1 (33%)	1 (11%)	1 (6%)	0 (0%)	2 (12%)	5 (8.8%)
C.C.U	4	8	10	7	6	4	39 (40%)
Deaths (Mortality rate)	1 (25%)	1 (12.5%)	4 (40%)	1 (14.3%)	2 (25%)	1 (25%)	10 (25 6%)
Total	7	11	19	24	16	21	98
Deaths (Mortality rate)	1 (14%)	2 (18%)	5 (26%)	2 (8.3%)	2 (12.5%)	3 (14%)	15 (15%)

C.C.U = Coronary care unit.

within six hours of the onset of infarction. Forty per cent of these patients were admitted to the coronary care unit, while 60 per cent were admitted to general hospital beds. While the over all mortality rate of this group was 15 per cent, there was a much higher relative mortality rate in the patients admitted to the coronary care unit. In the coronary care unit, there were 10 deaths, giving a mortality of 25.6 per cent, while of the hospital patients, there were only 5 deaths giving a mortality rate of 8.8 per cent. The mortality rate for the 160 patients admitted to hospital more than 6 hours after the onset of infarction was 30 per cent and this was significantly greater ($p > 0.025$) than the mortality rate of those patients admitted to hospital under 6 hours.

The average age of the patients admitted within 6 hours of the onset of severe pain was 55.5 years in the coronary care unit and 60.6 years in the ward beds. The mean age of the ten patients who died in the coronary care unit was 57.8 years, while the mean age of the 5 patients who died in ward beds was 64.2 years.

Table V details the clinical state of the patients at the time of their first examination after admission to hospital. The 258 patients are divided into the coronary care group and the hospital group and it can be seen that all the deaths in the coronary care unit were in patients who had persistent lung crepitations at the time of their first examination and in those patients with cardiogenic shock. In the hospital group 4 patients in whom there was no evidence of shock, crepitations, or elevation of the venous pressure, died while one patient who had only elevation of the venous pressure succumbed. The other patients who died in the hospital group were those with evidence of persistent crepitations at the lung bases on admission or in those in whom cardiogenic shock occurred.

Thus, the mortality rate for the hospital group excluding patients with "cardiogenic shock," is 17 per cent (27 of 163 patients) whereas for the similar coronary care unit group the mortality rate is 14 per cent (8 of 59 patients). In a previous report from the same hospital,[15] there was an 18 per cent mortality rate in patients treated in the coronary care unit and a 29.8 per cent mortality rate in patients treated in the general wards of the hospital when patients in cardiogenic shock were excluded.

Discussion

In previous reports from the Royal Melbourne Hospital we have described the

Table V Clinical severity in Classes 1 to 4 determined at time of admission

Hospital or C.C.U.	No shock crepitations or elevation of venous pressure	Persistent lung crepitations	Elevation of venous pressure	Cardiogenic shock	Total
Hospital	51	107	5	20	183
Per cent of group	28	60	3	12	
Deaths	4	22	1	17	44
Mortality rate (%)	8	20.6	20	85	24
C.C.U.	21	36	2	16	75
Per cent of group	28	48	3	21	
Deaths	0	8	0	10	18
Mortality rate (%)	0	17	0	62.5	24
Total (Hospital and C.C.U.)	72	143	7	36	258
Per cent of group	28	55	3	14	
Mortality rate (%)	5	21	14	75	24
Deaths	4	30	1	27	62

C.C.U. = Coronary care unit.

establishment of the coronary care unit.[7,12] There is little doubt that the recognition of cardiac arrhythmias at an early stage following acute infarction leads to more efficient treatment of patients with acute myocardial infarction. It is in this area of treating arrhythmias rapidly and efficiently that the coronary care unit has most clearly shown its effectiveness.[1-3] Long term survival following resuscitation from cardiac arrest occurring both in the coronary care unit and in ward beds attest to this improvement in medical management.[8,9,11]

While it is recognized that acute myocardial infarction is the main cause of premature death in the population of the developed countries, there is very little accurate information about the clinical course of the condition in patients whether they are managed inside a hospital or in the home. In this paper we have reported some of the information gained from registering all persons admitted to the hospital with a provisional diagnosis of acute infarction together with those patients found in the hospital to have suffered a myocardial infarction.

The patients registered were managed either in general ward beds or in a two-bed coronary care unit. We have analyzed certain characteristics of these two groups of patients separately and in so doing the differences between the groups have been highlighted. In emphasizing the difference between the patients it was noted that the coronary care unit received fewer female patients and that the average age of the patients admitted to the coronary care unit was significantly less than the age of the patients in the hospital ward beds. While one would not wish to put an age limit on admission to a coronary care unit, it seems not unreasonable to admit the younger patients to the unit.

Twenty-one per cent of the patients admitted to the coronary care unit had cardiogenic shock on admission compared with cardiogenic shock recorded in only 12 per cent of the patients admitted directly to a ward bed. These figures support the general concept that in many hospitals with a coronary care unit the policy is to admit the more seriously ill patients to the specialized unit, these tending to swamp the unit with seriously ill patients who may not obtain great benefit from special care. In this review the mortality rate in the shocked patients admitted to the hospital ward bed was higher than that among the patients admitted to the coronary care unit. This reflects some advantage in admitting the shock patient to the coronary care unit. However, the greatest value of the specialized coronary care unit relates to the treatment of the patients with acute infarction and cardiac arrhythmias and this value may be minimized by the unit receiving a very high proportion of patients with cardiogenic shock who only benefit to a small degree from the specialized treatment available in the coronary care unit. While it is beyond the scope of this report to make an objective assessment of the effectiveness of the coronary care unit in a hospital, it is considered that the maintenance of a register of patients coming into the hospital with acute manifestations of coronary artery disease will in due course make it possible to characterize those patients who will benefit most from being admitted to a specialized coronary care unit. This information will be of considerable value to those hospitals who are only able to maintain a small coronary care unit where a decision has to be made as to which type of patients should be admitted to the special unit.

Accepting at this time that most clinical and statistical evidence supports the contention that the coronary care unit provides an area in which a patient with acute infarction can be given more effective treatment, then we have to decide on the value of admitting all patients with acute infarction to such a unit. In our series of 278 patients registered in the six month period 258 were allocated in Classes 1 to 4 and would definitely qualify for admission to a coronary care unit. The additional 20 patients who were registered in Classes 5 to 6 would also qualify for admission once diagnosed. This makes an estimated total of 556 patients in one year. Assuming a relatively even distribution of admission over the 12 months the hospital would require a five-bed unit to keep each patient in the unit three days after admission

$$\left(\frac{\text{No of A.M.I.} \times \text{average no. of days in unit}}{365}\right)$$

Due to the uneven distribution of patients, however the unit would probably require an increment in beds of 25 per cent to cover the peaks of admissions.

In patients over the age of 60 years, there was no difference between the mortality rates of the two sexes. In patients under the age of 60 years, there was, however a noticeable difference in the mortality rate between the sexes with a significantly higher mortality rate in female patients. When a female under 60 years of age suffers *an acute myocardial* infarction there is more severe involvement with a greater risk of death.

The time of admission to the hospital *following infarction had a noticeable effect* on the hospital mortality rate. The patients admitted to hospital within six hours had a lower mortality rate than those admitted after six hours. This difference may be due to patients being admitted early (under six hours) because they had suffered an acute infarction and their medical advisor considered that they should be in the hospital while those patients admitted after six hours were referred because they had suffered a complication of acute myocardial infarction. It is interesting to note that there was a higher hospital mortality rate among those patients admitted to the coronary care unit within six hours of the onset of their severe pain. This observation reflects the tendency to admit the more seriously ill, younger patient to the coronary care unit particularly in the early stages after an acute myocardial infarction.

Review of the initial clinical presentation related to hospital mortality rate (Table V) shows that the patient with evidence of cardiac decompensation on admission to hospital has less chance of survival. This relationship was evident irrespective of whether the patient was admitted to a hospital ward bed or to the coronary care unit. The register highlights the need for improved treatment of heart failure in all patients. It is interesting to note that when one excludes patients with cardiogenic shock there does appear to be a reduction in mortality rate in patients treated in hospital wards from 29.8 per cent[13] to 18 per cent in the present report. While the method of identification of patients differed in the earlier report the mortality reduction suggests improvement in the management of patients with acute infarction not only in the coronary care unit, but also in the general *hospital* wards.

Registration may make it possible to detect, within a hospital population the form of treatment which will produce an alteration in survival. The data obtained from the registration of patients will help to provide a background of knowledge on which a rational plan of adequate hospital service can be *provided*. The establishment of coronary care units has given a suitable stimulus to the attempt to improve the management of patients with acute myo*cardial infarction. Initial published reports* from the units emphasized the value of the new concept, however it is now timely to examine the entire problem of the management of all patients presenting to the hospital with acute manifestations of coronary artery disease.

Since the first units were established in 1962[3], there have been important changes in the management of acute myocardial infarction with the introduction and wider use of drugs such as procainamide, propranolol and lidocaine for the treatment of cardiac arrhythmias. The development of more potent diuretic drugs and the more rational use of digitalis in the management of cardiac decompensation has also evolved. With the availability of these drugs, there has been a widespread change in emphasis from the treatment of cardiac arrest to its prevention by the earlier and more aggressive management of arrhythmias[4] coupled with the more enthusiastic treatment of patients with mild heart failure. It is against this background of changing therapy that the effectiveness of treatment of acute myocardial infarction should be assessed. It is considered that registration of patients within the hospital will indicate the areas where treatment still falls short and where it may be improved.

Summary

Registration of 278 patients admitted to the Royal Melbourne Hospital during

a six month period with definite or suspected acute myocardial infarction has been achieved One hundred and ninety nine patients were admitted to general ward beds while 79 patients were admitted to a two-bed coronary care unit. For the purpose of analysis registered patients were placed in one of the six diagnostic classes recommended by the World Health Organization A comparison of the patients admitted to hospital ward beds and to the coronary care unit emphasized the basic difference in the two groups of patients. The coronary care unit patients were younger they had a higher incidence of cardiogenic shock on admission and there was a higher mortality rate among those patients admitted to the unit within six hours of the onset of their severe pain The over all hospital mortality rate was 24 per cent in the patients admitted to the ward beds and to the coronary care unit. The register provides a background of information on which the effectiveness of the management of patients with acute myocardial infarction can be assessed

We thank the Medical Staff of the Royal Melbourne Hospital for permission to study patients in their care. We thank Miss Janice Ferguson who was responsible for the initial registration of all patients. We also thank Dr E. B Cross and Dr Ted Cooper of the United States Public Health Service for their continued support of the project

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Spread of activation in the anterolateral papillary muscle of the left ventricle of the dog under normal and pathologic conditions

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The clinical and electrocardiographic manifestations of dysfunction of the papillary muscle as well as some theoretic considerations of the mechanics of papillary muscle function under various conditions have been described.[1-4] Interest in the papillary muscle syndromes, especially in association with myocardial infarction, has been increasing. Other conditions such as hypertension, cardiomyopathies, valvular or other diseases, as well as myocardial infarction can lead to excess stress on the chordae tendineae and their area of attachment to the papillary muscles and cause rupture (particularly in the presence of fresh infarction) or fibrotic changes, especially near the tip and base of the muscle. The increasing number of publications concerned with the pathology of the papillary muscles during recent years indicates a recognition of their importance in health and disease.[4-]

Unfortunately, relatively little is known about the details of the anatomy, the circulation, the distribution of the Purkinje fibers, and the order of depolarization and repolarization of the papillary muscle.

From electrophysiologic experiments Scher and Young (also Scher[10,11]) suspected the existence of terminations of the Purkinje system deep in the walls of the myocardium at the attachments of the papillary muscles, which initiate the spread of activation simultaneously to the endocardium and epicardium. Hoffman and associates,[12] using endocardial bipolar leads, found that the wave of depolarization arrived at the papillary muscle–Purkinje tissue junction from more deeply located sites of attachment of the base of the papillary muscle.

The general and detailed pathways of activation in the heart muscle have been learned from experimental work of Scher [illegible]

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Durrer and Van der Tweel,[13] Sodi Pallares and associates,[14] and Erinzmetal and coworkers.[15,16] Publications of these investigators contain some data on the spread of activation in the papillary muscles. Scher and associates,[17] in studies of the right anterior papillary muscle, found points of very early activation near the tip of the papillary muscle. Their studies of the left anterior papillary muscle[9,18] revealed complicated patterns of excitation with reversal of directions of spread of activation with the wave progressing from a central point toward both the endocardium and epicardium. Activation in the area of the left posterior papillary muscle began under the papillary muscle and spread briefly toward both cavity and surface.[17]

Durrer and Van der Tweel[13] found that if the multiple electrode needle was situated in the papillary muscle in dogs, the electrodes close to the tip of the papillary muscle recorded activity progressing toward the cavity. The so-called "reversal phenomenon" (change in direction of the spread of the activation front) was commonly found in the papillary muscle.

Reports on the involvement of the papillary muscles during experimental localized ischemia are surprisingly scarce. Kline and associates[19] reported development of infarction of the anterolateral papillary muscle of the left ventricle of the dog after ligation of the third small branch of the anterior descending coronary artery distal to the perforating (septal) branch. Pathologic patterns of activation in the papillary muscles in dogs during experimental bundle branch block were reported by Scher's group.[20,21]

The scarceness and incompleteness of the available data on the spread of activation in the papillary muscles led us to study this portion of electrical activation of the heart. This report is concerned with the spread of activation in the left anterolateral papillary muscle of the left ventricle of the dog's heart under normal and pathologic conditions and the effect of experimentally produced ischemia of the anterolateral papillary muscle on the electrocardiogram (ECG), spatial vectorcardiogram (sVCG), and phonocardiogram (PCG).

Material and methods

The spread of activation in the anterolateral papillary muscle was studied under normal conditions in 30 healthy mongrel dogs weighing from 10.5 to 24.5 kilograms and under experimentally induced pathologic cardiac conditions in 23 otherwise healthy mongrel dogs weighing from 11.4 to 22.7 kilograms. Under Nembutal anesthesia, the chest was widely opened by a midsternal incision in some dogs and by incision in the fifth left intercostal space in others. Four multiple electrode needles were inserted simultaneously into the region of the left ventricle overlying the anterolateral papillary muscle. At the end of each experiment the heart was carefully removed and the locations of the multiple electrode needles and their electrodes in the papillary muscle, the area of its base, and adjacent portions of the free wall were carefully noted.

Three procedures were used for producing pathologic conditions in the heart.

1. *Acute local ischemia* was produced in 10 dogs (a) by ligating the left anterior ventricular branches of the anterior descending coronary artery and the anterior branches of the left circumflex coronary artery overlying and supplying the area of the wall of the left ventricle directly over the anterolateral papillary muscle or (b) by ligating the lower portion of the anterior descending coronary artery and its lower left anterior ventricular branch overlying the base of the papillary muscle, which supplied the apex of the heart and the area at the base of the anterolateral papillary muscle. These studies were continued for 4 or 5 hours after ligation.

2. *Ischemia of long duration with scarring* was produced in 6 dogs by ligation of the lower part of the anterior descending branch of the left circumflex coronary artery or of one of its left anterior ventricular branches overlying the left anterolateral papillary muscle. In these dogs, a small incision was made in the left side of the chest, which was closed after ligation was achieved. Studies were performed on these animals for 4 to 7 weeks after ligation.

3. *Focal inactivation and destruction of the myocardium* was produced in 7 dogs by injecting a solution of formalin and dye

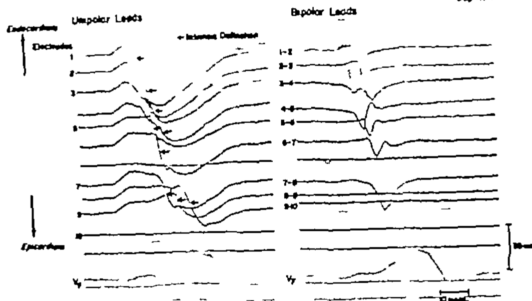


Fig. 1. Typical recording (this of Dog 56) of the spread of depolarization through the left anterolateral papillary muscle using unipolar and bipolar leads of multiple electrode needles. Lead V of the ECG was used for time reference. Electrode no. 1 was near the endocardium and no. 10 near the epicardium.

nto the area of the ventricular wall over the papillary muscle into the body of the papillary muscle, and into its base. Extension of infiltration by the formalin was determined approximately by the dye staining. These studies lasted 4 to 5 hours.

The intramural multiple-electrode needles were provided by Dr. D. Durrer*[13] and consisted of 7 to 10 electrodes mounted on a shaft with interelectrode distances of 1.66 to 3.0 mm.

The specially designed multichannel recorder employed in these studies had 15 cathode-ray tubes—12 for recordings directly from the heart muscle, one for the ECG Lead V, and 2 for the sVCG recordings of frontal and left sagittal plane projections. One millisecond time marks were obtained by interrupting the cathode beams. Spread of activation from one electrode to the next along one multiple electrode needle could be recorded simultaneously. Both bipolar and unipolar leads, in which the intrinsic deflection could be easily identified, were recorded directly as desired and used equally for analysis (Fig. 1).

Data were also recorded on a 14-channel magnetic tape recorder for more detailed study.

The beginning of deflection in the ECG Lead V correlated with the beginning of electrical activity in the recordings from the left ventricular cavity was used as the time reference for study of the spread of activation.

Serial electrocardiograms (ECG) and spatial vectorcardiograms (sVCG) were recorded during all studies and serial phonocardiograms (PCG) were recorded from dogs in which the coronary artery was ligated. Precordial leads were obtained only in dogs in which ligation was maintained for long periods.

Results

Spread of wave of activation

NORMAL ENDOCARDIAL SPREAD OF ACTIVATION. Data obtained from electrodes close to or directly in contact with the endocar

*We wish to thank Dr. D. Durrer, Professor of Cardiology, University of Amsterdam, and Director of the Department of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam, The Netherlands, for kindly supplying us with the multiple electrode needles.

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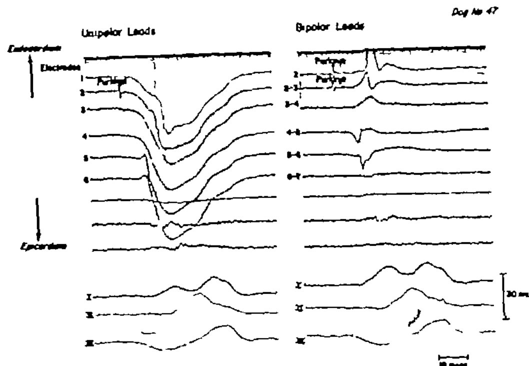


Fig. 3. Recordings of the e of depolarization (in Dog 47) through the left ventricular wall showing endocardial Purkinje fiber potentials at electrode no. 2 of the unipolar lead and between electrodes nos. 1 and 2 and nos. 2 and 3 in the bipolar leads.

areas, forming an island of relatively early activation with arrival times of activation ranging from 15 to 25 msec. The closely adjacent areas of the free left ventricular wall located over the tip of the papillary muscle or more laterally or toward the apex of the heart revealed arrival times of activation between 30 and 40 msec. after the beginning of ventricular activation (Fig 5)

NORMAL EPICARDIAL WAVE OF ACTIVATION The wave of activation arrived at the epicardium overlying the papillary muscle 20 to 35 msec. after the beginning of the cardiac electric cycle Areas located nearer the apex of the anterolateral papillary muscle or toward the lateral wall of the left ventricle or the base of the heart were activated later (up to 42 msec.) Earliest epicardial activation in the region of the papillary muscle was recorded on the septal sid of the left ventricular wall overlying the papillary muscle.

ACUTE MYOCARDIAL ISCHEMIA (FIG 6) Localization of ischemia-induced changes in electric activity was closely related to localization of the ligature. No significant delays were found in the time of arrival of the process of activation at the point of earliest activation in the papillary muscle. The influence of the pathology on the spread of activation in the anterolateral papillary muscle and adjacent ventricular wall was limited to the time interval between 6 and 12 msec. (earliest points at the endocardial surface) and between 20 and 30 msec. (latest points at the epicardial surface and at the tip of the papillary muscle) of the cardiac electric cycle. The total time of electric activity in the ventricles ranged from 45 to 60 msec. 2 hours after ligation of the coronary artery branch and up to 70 msec. 4 to 5 hours after ligation.

In the tracings obtained with bipolar (BP) leads, ischemia produced widening of the complexes with a decrease in voltage In the recordings from unipolar (UP) leads, reduction in amplitude of some of the intrinsic deflections was observed. The effect of ischemia on the general patterns of the time courses of the spread of activa

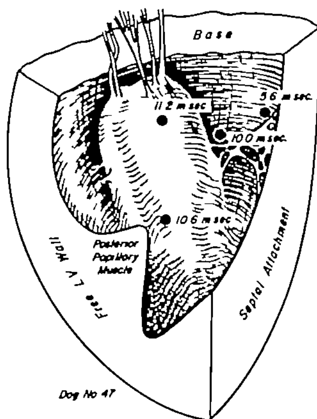


Fig 2 Sketch showing locations of 4 multiple electrode needles (black dots) and the recorded times of arrival of the wave of depolarization at various points on the endocardial surface of the left anterolateral papillary muscle of Dog 47 The times in milliseconds are measured from the onset of ventricular depolarization. The depolarization process spread from the septal side toward the free wall of the left ventricle and from the base toward the apex of the papillary muscle.

dial surface indicated that the wave of activation progressed from the septal side toward the free wall of the left ventricle enveloping on its way the endocardium of the papillary muscle from the septal to the lateral side (Fig 2) At the same time the endocardial wave of activation spread from the base toward the apex of the papillary muscle. The rate of this spread ranged from 1 25 to 2 0 M per second (assuming that there was uniform spread in one direction) with several simultaneous points of activation being observed

Activation of the endocardium covering the left anterolateral papillary muscle occurred from 5 to 15 msec. after the beginning of ventricular activation as estimated from Lead V_F and intracavitary leads. The arrival time of activation at various endocardial locations at the base of the papillary muscle was between 5 and 9 msec. between 5 and 8 msec. in the groove between the septum and the papillary muscle between 10 and 13 msec. on the septal side of the papillary muscle, between 11 and 13 msec on its central surface (facing the left ventricular cavity) between 13 and 15 msec on its lateral surface (facing the free lateral wall of the left ventricle) and between 14 and 20 msec. near the tip of the papillary muscle

In two experiments Purkinje potentials were recorded with the electrodes which were in contact with the endocardium over the papillary muscle (Fig 3) They preceded the intramural complexes by 12 to 14 msec.

NORMAL SPREAD OF ACTIVATION WITHIN THE BODY OF THE PAPILLARY MUSCLE. Some central portions of the papillary muscle were activated at the same time as or even before the endocardial points. For example activation as early as 5 msec. after the beginning of ventricular activation was observed Complete activation of the central portions of the papillary muscle was accomplished during a relatively short period of time i e up to 5 msec whereas the spread of activation over an equal distance in the free overlying ventricular wall required up to 20 msec. (Fig 4) The calculated velocity of spread of activation was about 1 M per second in the central portions of the papillary muscle and about 0 3 M per second in the free wall at the base of the papillary muscle.

Other areas of early activation were found at the base of the papillary muscle and in the area of its attachment to the ventricular wall The areas of the papillary muscle activated latest were near its tip. In a few dogs, however these locations showed very early endocardial activation whereas in others the activation of this area was much delayed possibly due to damage of the conduction or circulatory system during the insertion of the electrodes.

It was also noted that the spread of activation in the portions of the left ventricular wall directly overlying the papillary muscle and in the vicinity of its base was faster than in the adjacent portions of the free left ventricular wall The activation was also completed much earlier in these

Dog No. 66

Multiple Electrode Needle No. 3

Multiple Electrode Needle No. 1

Fig. 5. Variations in the rate of speed of activation in the left anterolateral papillary muscle and in the free left ventricular wall overlying the papillary muscle of Dog 66.

with scarring were usually not extensive. Cross pathologic examination revealed diffuse patchy discolorations on the cross section and sometimes small well-defined scars.

Changes in spread of activation in the myocardial tissue in the area of the ligated artery sometimes resulted in disappearance or reduction of the magnitude of the intrinsic deflection in the unipolar leads with persistence of the remaining portion of the deflection. Bipolar leads revealed a marked decrease in magnitude of voltage or total loss of measurable voltage. In other instances the complexes recorded were wide and irregular with multiple deflections of low amplitude.

The velocity of spread of the wave of activation in the regions containing the disseminated scar tissue was about half that in normal tissue. The activation of the papillary muscles and the overlying portions of the wall of the left ventricle was completed between 8 and 30 msec. after the beginning of ventricular electric activity. This time was prolonged to 36 msec. in the instance of involvement of the portion of the free wall of the left ventricle overlying the tip of the papillary muscle with resultant decreased velocity of the spread of activation in regions of scarred tissue.

Depending upon the location of the endocardial electrode in the papillary muscle endocardial activation began 8 to 13 msec. after the beginning of ventricular activity. The wave of activation appeared at the

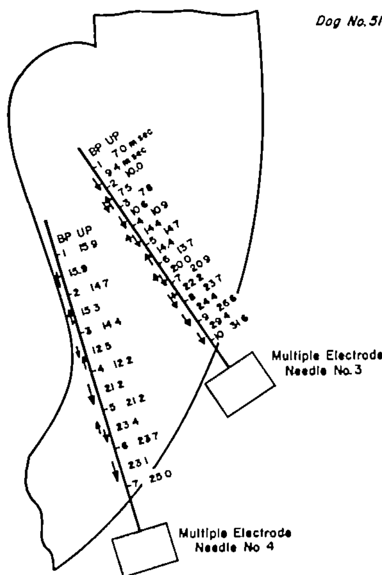


Fig 4 Variation in the spread of activation in the left anterolateral papillary muscle of Dog 51 The sketch shows the positions of electrode needles no 3 (with 10 electrodes) and no 4 (with 7 electrodes) in the left ventricular wall and anterolateral papillary muscle In this and all other similar figures, the arrival times of activation along the multiple electrode needle are noted in millisecond near both unipolar (*UP*) and bipolar (*BP*) leads of the needle. The earliest point of activation was at the base of the papillary muscle (electrode no. 4 of needle no 4) The direction of spread of activation is indicated by the arrows; double arrows represent biphasic complexes.

tion was extremely variable, with areas of reversal of the directions of spread and local delays or accelerations in time of arrival of activation Local delays in arrival time ranged up to 2 5 msec in the body of the papillary muscle and up to 8 msec. in the overlying ventricular wall when compared with the control recordings. Delays in time of arrival from that for the normal also ranged up to 8 msec at the tip of the papillary muscle when most of the papillary muscle was made ischemic Sometimes the time of arrival of the process of activation at the epicardial surface was accelerated up to ? msec The average velocity of the spread of activation in areas modified by ischemia was about half that for normal areas. The decrease in the rate of spread of activation was more pronounced in the wall of the left ventricle than in the papillary muscle itself No changes in the general direction of the spread of activation were observed in the anterolateral papillary muscle of the left ventricle nor was complete disappearance of local electric activity recorded

ISCHEMIA OF LONG DURATION WITH SCAR FORMATION (FIG 7) The areas of ischemia

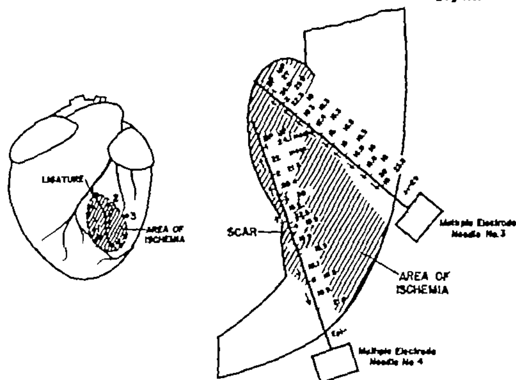


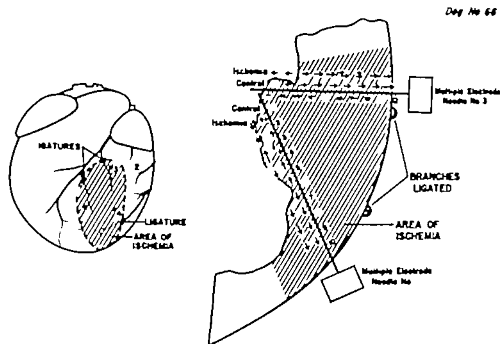
Fig 7 Effect of experimentally induced ischemia of long duration (7 weeks) with scarring on the spread of activation in the left anterolateral papillary muscle and overlying free wall of the left ventricle of Dog 64.

ward the deeper portions of the myocardium.

Following injection of formalin the heart rate usually decreased by about 20 per cent and the total time of ventricular activation increased up to 70 msec. The observed pathologic disturbances in electric activation were limited to the time interval between 7 and 36 msec. after the beginning of the QRS complex Thus, these data indicate the time within the electric cycle that the papillary muscle is activated

VENTRICULAR PREMATURE CONTRACTIONS Aberrant spread of activation in the anterolateral papillary muscle of the left ventricle of the dog's heart during premature ventricular contractions included three essential patterns (1) activation initiated in the area of the tip of the papillary muscle with continuous spread from endocardium to epicardium (2) activation initiated by stimulation of the epicardium or a point near the epicardium with continuous spread of activation from epicardium to endocardium and (3) activation initiated lateral to the papillary muscle with the wave of activation arriving perpendicular to the long axis of the papillary muscle (along the endocardium or along the superficial subendocardial layers of the myocardium)

With the first type (Fig 9) the earliest activation recorded along the multiple electrode needle occurred 5 6 msec. after the beginning of ventricular activation The spread of the wave of activation seemed to be relatively smooth continuous and uniform except in a small area at the attachment of the papillary muscle to the ventricular wall (Fig 9 between electrodes 4 and 6) The front of the wave of activation arrived at the subepicardial electrode 45 msec. after its onset. The total duration of ventricular activation as calculated from the electrocardiogram was 103 msec. The mean velocity of the spread of the wave of activation was 0.38 M. per second as opposed to 0.56 M per second during normal ventricular contraction in the same



Electrodes	Mult Elect Control BP	Mult Elect Control UP	Needle #3 Ischemia BP	Needle #3 Ischemia UP	Mult Elect Control B	Mult Elect Control UP	Needle #1 Ischemia BP	Needle #1 Ischemia UP
				[illegible]				
	[illegible]		[illegible]				[illegible]	
2		14		[illegible]		17		17
	[illegible]		[illegible]		13		[illegible]	
3		[illegible]		10		13		[illegible]
							14	
				[illegible]		14		[illegible]
							[illegible]	
5								[illegible]
			[illegible]				10	
6		[illegible]		14				
	[illegible]		24					
		[illegible]		[illegible]				
							[illegible]	
8		24		24		[illegible]		12
	24		[illegible]		[illegible]		[illegible]	
		30		[illegible]				[illegible]
	[illegible]		30				15	
10		[illegible]		[illegible]		[illegible]		

Fig *6* Effect of experimentally induced acute ischemia (shaded areas) on the recorded spread of depolarization in the left anterolateral papillary muscle and the left ventricular wall overlying the papillary muscle of Dog 66.

epicardium in the area of the papillary muscle between 20 and 36 msec. after the beginning of ventricular electric activity The total activation time of the ventricles ranged up to 73 msec In a case in which ischemia involved most of the papillary muscle the arrival of activation at the tip of the papillary muscle was as late as 27 msec after the beginning of ventricular electric activity (Fig 7) At the same time a scar at the base of the papillary muscle caused almost complete disappearance of electric activity in this area and the bipolar leads showed widening of the complexes.

LOCAL INFILTRATION WITH FORMALIN (FIG 8) Infiltration of the papillary muscle with formalin produced marked reduction in or complete disappearance of deflections in recordings with both the BP and UP leads. An interesting finding was the reduction of voltage of the cavitary leads recorded from those electrodes in the vicinity of the damaged myocardium When some local activity persisted reversals of the spread of the front of activation over limited areas of the myocardium were observed Delays ranged up to 4 msec. in the spread of activation from the earliest activated points in both directions, i e. toward the cavity and toward the epicardium Sometimes in instances of severe and extensive damage at the base of the papillary muscle the general direction of spread of the wave front of activation was reversed from the normal (endocardium to epicardium) to invasion from the epicardium to-

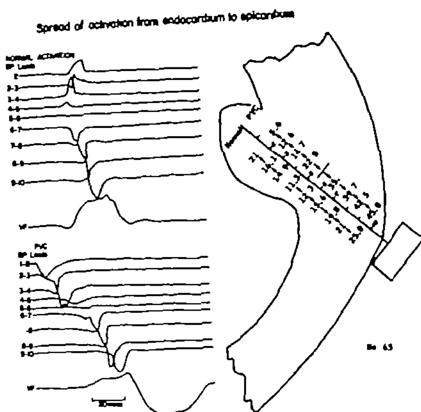


Fig. 9 Spread of activation in the left anterolateral papillary muscle of Dog 65 during premature ventricular contraction (*PVC*) in which activation was initiated near the tip of the papillary muscle and spread in direction from the tip toward the epicardium overlying the base of the muscle. Consult text.

mately 50 msec The average velocity of the spread of activation along the multiple electrode needle was 0.38 M per second (0.48 M per second in the body of the papillary muscle and 0.33 M per second in the wall of the left ventricle at the base of the papillary muscle)

In the same experiment, another type of premature ventricular contraction was observed (Fig 10 PVC I) which had the same general direction of spread of activation and essentially the same arrival times and calculated velocity of spread (0.32 M per second) for the portion of the multiple electrode needle in the wall of the left ventricle at the base of the papillary muscle as described for the previous type of premature ventricular contraction (PVC II) However the velocity of the spread of activation in the body of the papillary muscle for PVC I was much greater than for PVC II being in the order of 1 76 M per second It is possible in this instance that the wave of activation somewhere along its course (possibly in the area of electrode no 6) was conducted part way along the body of the papillary muscle through segments of the conduction system which became excited. The two premature ventricular contractions described above appeared successively on the electrocardiographic recording

During the third type of premature ventricular contraction the wave of activation arrived at the electrodes located in the body of the papillary muscle between 32.8 and 33 1 msec. after the beginning of ventricular activation and in the wall of the left ventricle at the base of the papillary muscle between 32.8 and 34 7 msec. (Fig 11) Judging from the localization of the multiple electrode needle in the base of the papillary muscle with subepicardial electrodes being more lateral, and from their later

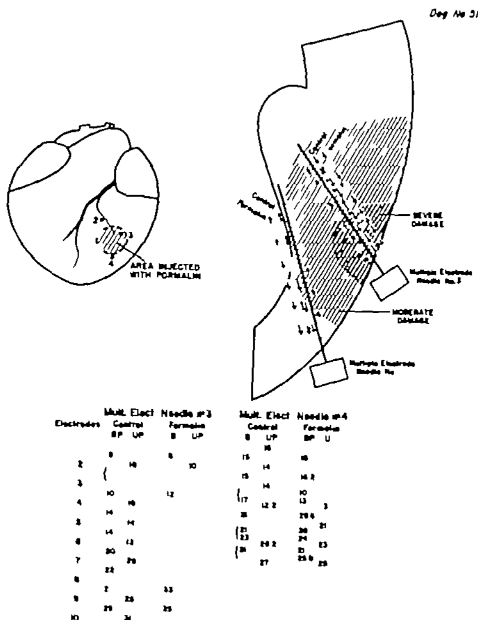


Fig 8 Effect of damage produced by local injection of formalin in the area of the left anterolateral papillary muscle on the spread of activation in the papillary muscle and the damaged myocardium of Dog 31

dog The velocity of the spread of activation during premature ventricular contraction calculated for the portion of the electrode needle in the body of the papillary muscle was 0 40 M per second and along the portion of the electrode needle in the wall of the left ventricle at the base of the papillary muscle was 0 66 M per second (under normal conditions it was 0 56 M per second for both) This difference was based on the simultaneous spread of activation in the direction of the tip of the papillary muscle and in the direction of epicardium at the base of the papillary muscle seen under normal conditions (Fig 9 normal)

With the second type of premature ventricular contraction (Fig 10 PVC II) the earliest activation as recorded by the subepicardial electrode occurred 7 5 msec after the beginning of ventricular electric activity The progression of the wave seemed to be smooth and uniform in the direction of the tip of the anterolateral papillary muscle of the left ventricle Again a small decrease in the velocity of spread was noticed in the area near the attachment of the papillary muscle to the ventricular wall (Fig 10 electrodes 5 to 7) The latest activated point at the tip of the papillary muscle was recorded at approxi

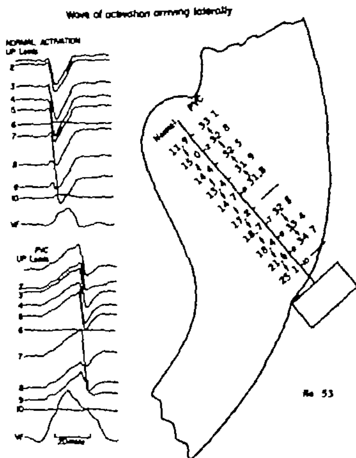


Fig. 11 Spread of activation in anterolateral papillary muscle of Dog 53 during a premature ventricular contraction in which activation was *initiated lateral* to the papillary muscle and *spread in direction perpendicular* to the long axis of the papillary muscle as indicated by the almost simultaneous activation at all electrodes

When the pathologic process involved to a greater extent the body of the papillary muscle as a result of ligation of coronary branches closer to the apex of the heart *(terminal portion of the anterior descending* coronary artery) the changes were an increase of positivity of the T waves in Leads II III and V with accompanying depression of the ST T segment and an increase of the negativity of the T wave in Lead V with accompanying elevation of the ST T *segment* (Fig 13)

The changes observed in the serial precordial leads recorded in experiments with chronic ligation were increased positivity of the T waves with temporary depression of the ST T segment in Leads V to V (Fig 14)

Particularly marked abnormalities of the ECG followed damage of the myocardium induced by local injection of formalin (Fig 15) The extent of this damage was usually greater than damage *produced by ligation of the coronary* arteries.

Spatial vectorcardiograms Frontal and left sagittal plane projections of vector cardiograms were recorded with the tetrahedral reference system.[12] Changes caused by ligation or local damage induced by the injection of formalin were not extensive (Fig 16) In some experiments with the formation of scar slight widening of the QRS sÊ-loops, increase in magnitude of the late portions, or appearance of a small initial portion of the QRS sÊ loop oriented directly above the horizontal plane was observed. QRS *sÊ loops in other dogs re-*

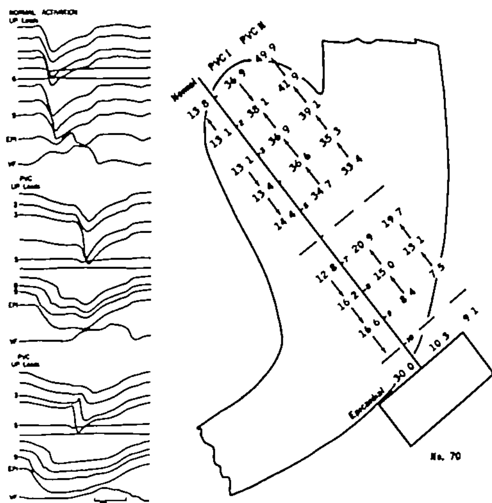


Fig 10 Spread of activation in the left anterolateral papillary muscle of Dog 70 during two successive premature ventricular contractions in which activation was initiated at the epicardium at the base of the papillary muscle and spread in direction from the epicardium to the tip of the papillary muscle Consult text.

activation it seems that the wave of activation arrived from the direction of the ventricular septum The calculated velocities of the spread of activation during normal activation were 1 32 M per second for the total length of the electrode needle 0 94 M per second for the body of the papillary muscle and 0 50 M per second for the wall of the left ventricle at the base of the papillary muscle These high values indicate that the wave front of activation approached the multiple electrodes under normal conditions in a direction that formed an angle with the long axis of the multiple electrode needle.

Electrocardiograms Typical electrocardiograms are presented in Figs. 12 to 15 Analysis of the QRS complexes did not reveal any significant abnormalities due to the induced pathologic states. The observed changes involved primarily the ST T segment and T wave Two types of abnormalities were observed and the recorded patterns were affected by the location and extent of induced myocardial damage

With ligation of the coronary branches overlying the anterolateral papillary muscle (left ventricular branches of the anterior descending coronary artery) and with damage limited mainly to the base of the anterolateral papillary muscle and to the portion of the wall of the left ventricle overlying the body of the papillary muscle the most pronounced changes were the appearance of negative T waves in Leads II III and V_F and depression of the STT segment in the same leads (Fig 12)

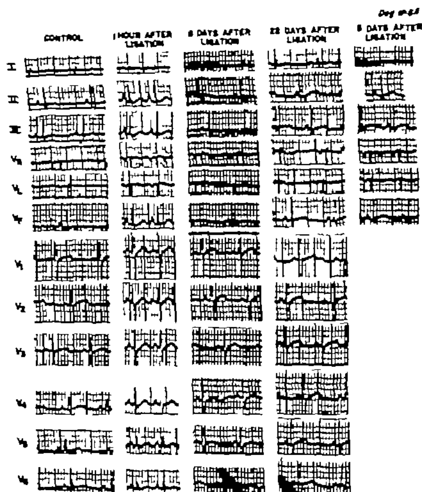


Fig 14 Effect on the ECG of chronic ischemia of the left terolateral papillary muscle (prolonged ligation of coronary artery branch.)

vealed small slurrings or notchings of the initial portion of the QRS sÊ-loop i.e. before the point of maximal deflection (time interval corresponding to the activation of the anterolateral papillary muscle) It was difficult to evaluate changes in the magn tude of the maximal mean nstantaneous vector of the QRS sÊ-loops because of the coexistence of hanges due to position.

More pronounced hanges were observed in th T sÊ loops Vectorcardiogr ms re- orded n experiment w t acute ischemia or njection of formalin rev led t t sea a slight decre se or ncrease (Fig 16) of the magn tude of t ma m l mean in- stantaneous ectors of the T sÊ loops or a slight increase in the magnitude of th angle between the maximal mean instan taneous vectors of the QRS sÊ and T sÊ loops.

Phonocardiograms In most experiments PCG s were recorded directly from the free wall of both ventricles, pulmonary and aortic infundibulae, and the base of the anterolateral papillary muscle of the left ventricle In dogs in which ligation was maintained for several weeks, serial PCG s from the chest w ll were also recorded Following ligation of the coronary artery or injection of formalin there was a ma ked transitional decrease in intensity of the heart sounds Occasionally a loud sy tolic murmur followed insertion of the multiple electrode needle into the papillary

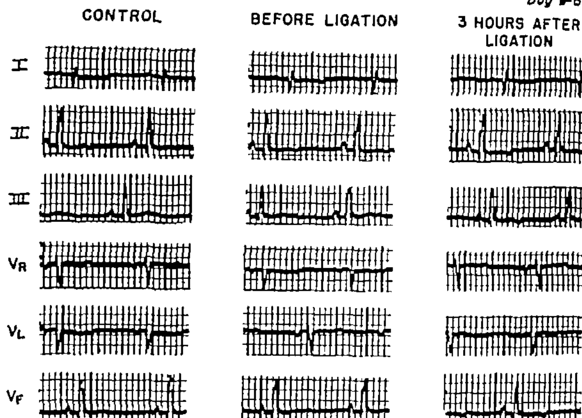


Fig 12 Effect on the ECG of acute ischemia limited mainly to the base of the *left anterolateral papillary muscle* and the portion of left ventricular wall overlying the body of the papillary muscle. The changes primarily involved the T waves and ST T segment In this and the following figures, the control ECG was recorded after the dog chest was opened

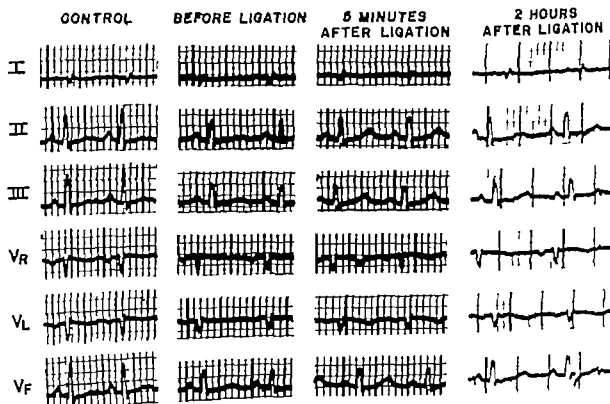


Fig *13* Effect on the ECG of acute ischemia involving mainly the body of the left anterolateral papillary muscle.

muscle and from areas at its base and at its attachment to the left ventricular wall. The resulting waves of activation progressed in endocardial direction in the papillary muscle and in epicardial direction in the overlying wall of the left ventricle. Thus, the activation of the papillary muscle resulted from the simultaneous spread of the wave of activation from the endocardium and most probably from the terminations of the Purkinje system located deep in the papillary muscle and at its base. Relatively large areas of almost simultaneous excitation with reversals of polarity of the recorded leads seen by us in the central portions of the papillary muscle and also observed by Durrer and Van der Tweel[12] seem to confirm that there is an abundant distribution of Purkinje fibers in this region

The adjacent regions of the free left ventricular wall were activated uniformly in the direction from endocardium to epicardium

The midportion of the lateral septal aspect of the papillary muscle surface is of particular interest. Careful inspection during sectioning revealed the existence of threadlike structures which emerged from the septum in the area of its attachment to the anterior left ventricular wall traversed the cavity freely and entered the papillary muscle. These filamentous structures, also observed previously by us[3] and others,[22,23] were found to originate subendocardially in the upper part of the septum in the region of the aortic valve where they seemed to emerge from deeper layers of the muscular tissue. Similar structures entered the posteroseptal papillary muscle. It has been assumed that these structures carry small branches of conductive tissue Measurements of the activation time in the papillary muscle seem to support this assumption. An anatomic study would be needed however to confirm fully this assumption. Estes and associates[23,24] and we[3] found that the threadlike structures which connect the papillary muscles with the free wall of the ventricle in human hearts may occasionally carry vascular channels to the papillary muscles.

The total time of electric activation of the anterolateral papillary muscle of the left ventricle ranged from 5 to 10 msec. and corresponded to a time interval between 5 and 20 msec. of the ventricular electric activity The total ventricular activation time in the dogs studied ranged from 45 to 60 msec. If mechanical events follow electric activation by the same time interval in all portions of the heart muscle, a relatively early contraction in the papillary muscle during the early phase of cardiac cycle is indicated. Relatively early activation occurred also in the area of attachment of the papillary muscle to the left ventricular wall whereas the adjacent portions of the free left ventricular wall were activated much later Relatively deep penetration of the Purkinje system into the left ventricular wall overlying the papillary muscle is suspected.

The process of activation at the papillary muscle was essentially unchanged by the induced pathologic states. The total time of activation of the papillary muscle was occasionally prolonged but it was usually associated with increased total time of activation for all of the two ventricles. The observed abnormalities included local decrease in or disappearance of electric activity or local reversals of direction of spread of the process of electric activation General patterns of direction of spread of activation however were changed relatively little when compared to normal. Occasionally islands of reversed direction of propagation of the wave of excitation i.e., from epicardium toward the deeper myocardial layers, were observed at the base of the papillary muscle. The observed abnormal patterns of spread of the process of activation were not uniform and thus correlated well with nonuniform anatomic changes found on direct examination of the injured heart. When a delay in arrival or diminished velocity of the spread of the wave of activation was observed it was much more pronounced in the free wall of the left ventricle overlying the papillary muscle than in the anterolateral papillary muscle itself This observation tends to indicate that the conductive tissue is more abundant in the papillary muscle and that its penetration into the overlying ventricular wall is rather poor Furthermore the conductive tissue seemed to be in

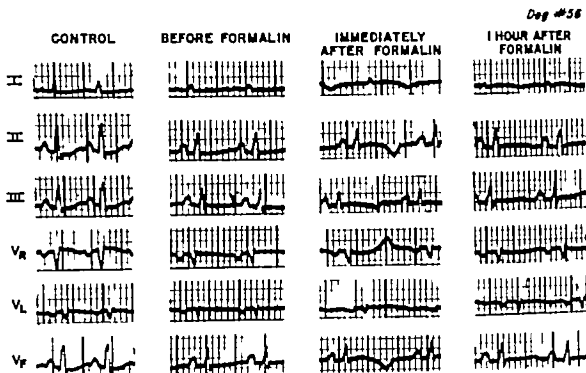


Fig. *15.* Effect on the ECG of ischemia of the left anterolateral papillary muscle following injection of formalin.

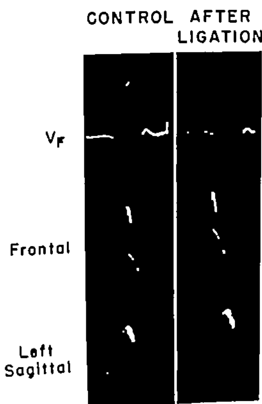


Fig. *16.* Effect on the sVCG (Dog 69) of acute ischemia of the left anterolateral papillary muscle. The changes were slight and primarily involved the sÊ-loop.

muscle. However, on direct auscultation from the heart, the murmur was audible only at the area of the wall of the left ventricle directly overlying the base of the anterolateral papillary muscle. The intensity of the murmur rapidly diminished toward the septum or toward the lateral wall of the left ventricle. The recorded murmurs were usually of low intensity, and in only a few experiments did a distinct systolic murmur follow the ischemia or formalin damage to the area of the papillary muscle.

Discussion

This study of the spread of activation in the anterolateral papillary muscle of the left ventricle revealed that the endocardial wave of activation approaches the papillary muscle from the side of the interventricular septum and spreads over the endocardium covering the papillary muscle in the direction from the septum toward the free left ventricular wall and simultaneously from the base to the apex of the papillary muscle.

In addition to the spread of activation from the endocardium into the deeper subendocardial layers, there was a simultaneous spread of activation from areas in the center of the body of the papillary

muscle and from areas at its base and at its attachment to the left ventricular wall The resulting waves of activation progressed in endocardial direction in the papillary muscle and in epicardial direction in the overlying wall of the left ventricle. Thus, the activation of the papillary muscle resulted from the simultaneous spread of the wave of activation from the endocardium and most probably from the terminations of the Purkinje system located deep in the papillary muscle and at its base. Relatively large areas of almost simultaneous excitation with reversals of polarity of the recorded leads seen by us in the central portions of the papillary muscle and also observed by Durrer and Van der Tweel[illegible] seem to confirm that there is an abundant distribution of Purkinje fibers in this region.

The adjacent regions of the free left ventricular wall were activated uniformly in the direction from endocardium to epicardium.

The midportion of the lateral septal aspect of the papillary muscle surface is of particular interest. Careful inspection during sectioning revealed the existence of threadlike structures which emerged from the septum in the area of its attachment to the anterior left ventricular wall, traversed the cavity freely and entered the papillary muscle. These filamentous structures, also observed previously by us[4] and others,[illegible] were found to originate subendocardially in the upper part of the septum in the region of the aortic valve where they seemed to emerge from deeper layers of the muscular tissue. Similar structures entered the posteroseptal papillary muscle. It has been assumed that these structures carry small branches of conductive tissue.[illegible] Measurements of the activation time in the papillary muscle seem to support this assumption. An anatomic study would be needed however to confirm fully this assumption Estes and associates[illegible] and we[4] found that the threadlike structures which connect the papillary muscles with the free wall of the ventricle in human hearts may occasionally carry vascular channels to the papillary muscles.

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The process of activation at the papillary muscle was essentially unchanged by the induced pathologic states. The total time of activation of the papillary muscle was occasionally prolonged but it was usually associated with increased total time of activation for all of the two ventricles. The observed abnormalities included local decrease in or disappearance of electric activity or local reversals of direction of spread of the process of electric activation General patterns of direction of spread of activation however were changed relatively little when compared to normal Occasionally islands of reversed direction of propagation of the wave of excitation i e from epicardium toward the deeper myocardial layers, were observed at the base of the papillary muscle. The observed abnormal patterns of spread of the process of activation were not uniform and thus correlated well with nonuniform anatomic changes found on direct examination of the injured heart. When a delay in arrival or diminished velocity of the spread of the wave of activation was observed it was much more pronounced in the free wall of the left ventricle overlying the papillary muscle than in the anterolateral papillary muscle itself This observation tends to indicate that the conductive tissue is more abundant in the papillary muscle and that its penetration into the overlying ventricular wall is rather poor Furthermore the conductive tissue seemed to be in-

fluenced relatively little by the ischemia produced in these studies as indicated by essentially no delay in the initiation of the process of activation in the anterolateral papillary muscle of the left ventricle under pathologic conditions.

It was extremely difficult to achieve complete and uniform ischemia of the anterolateral papillary muscle in each dog despite the ligation of all accessible arterial branches supplying this area In some experiments in which the left anterior ventricular branches (first second and sometimes third) of the anterior descending coronary artery directly overlying the anterolateral papillary muscle of the left ventricle were ligated the resulting ischemia involved mainly the ventricular wall over the papillary muscle at its base The ischemic damage to the papillary muscle itself was not extensive In other experiments in which the ligated branch was the terminal portion of the anterior descending branch of the left circumflex coronary artery and sometimes the lower left anterior ventricular branch of the anterior descending branch of the left circumflex coronary artery the ischemic area included the base of the papillary muscle the papillary muscle itself and the ventricular wall over the papillary muscle and extended to the apex of the heart However complete ischemia of the entire papillary muscle was not always attainable Collateral blood supply from deeply buried arterial branches was suspected This is well supported by studies in man [4]

The anatomicopathologic examination revealed incomplete ischemia of the papillary muscle even when all accessible sources of blood supply to the papillary muscle were occluded In these instances the blood was supplied to the papillary muscle by other more remote or deeply buried collateral arterial branches. Recent findings by us[4] and by Estes and co-workers[22,23] revealed the existence of very well-developed subendocardial arterial plexus with rich and large anastomoses and of vascular channels in some of the transventricular filamentous structures. These findings explain the additional blood supply to the anterolateral papillary muscle and the difficulties observed by us in producing complete ischemia of the papillary muscle.

Although a frequent finding during postmortem examination of human hearts is scarring at the apex of the anterolateral papillary muscle of the left ventricle, we observed no scarring in chronic experiments in the dogs. One wonders whether this particular location of scars in human hearts is due to peculiarities of its blood supply or other factors.

Three different directions of arrival and rates of spread of the abnormal wave of excitation in the papillary muscle resulting from premature ventricular contraction were found depending primarily upon the site of initiation of the impulse When activation started in the area of the tip of the papillary muscle its progression through the body of the papillary muscle was somewhat slower than through the wall of the left ventricle at the base of the papillary muscle (0 40 and 0 66 M per second respectively) On the other hand when the excitation started in the subepicardial layers at the base of the papillary muscle it progressed somewhat faster through the body of the papillary muscle (0 48 and 0 33 M per second respectively) In both instances, however the velocities of the spread of the wave of activation in the body of the papillary muscle were quite similar (0 40 and 0 48 M per second for the entire body) and were only slightly higher than those calculated for the conduction velocity in the myocardium (0 3 to 0 4 M per second) [22,23] The velocity of spread of activation in the first instance was significantly higher in the wall of the left ventricle (0 66 M per second) than the normal values mentioned above This relatively high velocity is most probably artifactual from calculations because of an angular direction of approach of the wave front of activation with the long axis of the multiple electrode needle This factor must be considered in studies of the spread of activation in the papillary muscles since it is difficult to locate the electrode needle exactly in the middle of the papillary muscle and precisely along its long axis. Furthermore there are other connections to the wall of the ventricle through which activation can occur

In the instance where a premature ventricular contraction invaded the papillary muscle and a high velocity of the spread of the wave of activation was found in the body of the papillary muscle, it appeared that the wave of activation excited the Purkinje system after traversing the myocardium nea the base of the papillary muscle. This observation is supported by studies of Scher[17] in which the velocity of the spread of the wave of activation in the Purkinje fibers was found to be between 1.0 and 2.0 M per second

Because t is extremely difficult to be certain of the precise direction or spatial contour of the wave front of the activation process, it is impossible to measure exactly the rate of spread of activation with such preparations as used in these studies. Thus, the rates indicated n these experiments can only be close approximations.

Electrocardiograms and spatial vectorcardiograms ecorded during experiments of induced ischemia of the anterolateral papillary muscle of the dog s left ventricle revealed little influence of the induced pathologic states on the QRS complex of the ECG or on the QRS sÊ loop of the sVCG It is apparent that activ ty from other portions of the heart camouflaged the local loss of electric activity On the other hand the damage was well displayed by the repolarization complexes of the ECG and VCG Shifts of the ST T segment changes n the magnitude and direction of the T wa e and T sÊ-loop and changes in the ngle between the maximal mean instantaneous vectors of the QRS Ê and T sÊ loops were produced

Relatively l ttle abnormal ty was found in the phonocardiograms recorded either directl from the heart or from the chest wall This is probably du to the fact that because of efficient collateral circulation in the dog the extent of ischemia or damage produced in our experiments was not sufficient t cause relat v m tral v lvular insufficiency to produce murm ur in every do.

Summary

The spread of electric activ tion in the anterolater l papillary muscle of the left ventricle was studied in 30 dogs under normal conditions and in 23 dogs under the influence of induced ischemia using multiple-electrode needles as well as during premature ventricular contractions. The effects of induced ischemia on the electrocardiogram spatial vectorcardiogram and phonocardiogram were also studied

The endocardial wave of activation was found to approach the papillary muscle from its septal side and spread in the di rection toward the free left ventricular wall and toward the apex of the papillary muscle

The anterolateral papillary muscle of the left ventricle was activated simultaneously by the penetration of wave fronts (1) from the endocardium into deeper portions of the papillary muscle and (2) from the central portions of the papillary muscle and from the area of its attachment to the left ventricular wall

The shorter time needed for the excitation wave to arrive at the epicardium in areas of left ventricular wall overlying the papillary muscle and the higher calculated velocity of spread in these areas indicate more abundant penetration of Purkinje tissue than in the adjacent portions of the free left ventricular wall

The pathologic influence on the spread of activation in the papillary muscle was lim ted to the time nterval between 6 and 36 msec of the cardiac electric cycle with no significant delays in the time of arrival of the process of activation at the points of earliest activation w thin the papillary muscle or at ts endocardial surface Ischemia and injection of formalin produced local decrease or disappearance of electric activity and local reversals of the direction of spread of activation in limited portions of the papillary muscle or in the overlying wall of the left ventricle

Three types of aberrant spread of activation in the papillary muscle during premature ventricular contractions were described

No major changes were observed in the QRS complexes of the ECG or QRS sÊ loops of the sVCG in dogs w th experimentally induced ischemia. The changes n olved predom nantly the repolarization phase of the ECG and sVCG Phonocardiograms occasionally revealed a loud systolic

murmur which followed immediately the insertion of the multiple electrode needle into the papillary muscle.

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A new mechanocardiographic index in evaluation of the severity of mitral stenosis: An apexcardiographic study

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In a previous work the author demonstrated the superiority of the C-1 interval over the Q-1 interval in the diagnosis of mitral stenosis. The C-1 interval represents the initial phase of ventricular contraction measured from the onset of the systolic wave (C point) on the apexcardiogram to the main vibrations of the first mitral sound in the phonocardiogram (Figs. 5 and 6). The C-1 interval shows the actual delay of the first sound while the diagnostic value of the transformation time (Q-1 interval) is diminished by the included electromechanical delay which varies between 10 and 70 msec. in patients with mitral valve disease.

Along with that, a significant correlation has been established by the author[8] between the duration of the rapid filling wave (O-F interval) on the apexcardiogram (Fig. 5) and the long diameter of the mitral orifice. In most patients with mitral stenosis the rapid filling wave on the apexcardiogram is absent or significantly reduced.[1, 10]

Both time intervals (C-1 and O-F) are closely related to the mitral valve size, the C-1 interval being directly proportional and the O-F interval inversely proportional to the degree of mitral stenosis.[3] Hence the difference between these intervals may be used as a mechanocardiographic index in evaluation of the severity of mitral stenosis.

The search for new and more reliable mechanocardiographic methods in evaluation of the severity of mitral stenosis is justifiable in view of the increasing tendency of using indirect methods for this purpose, when possible.

Methods

Studies were done on 70 patients with mitral valve disease. There were 52 women and 18 men. The patients' ages ranged from 16 to 56 years with a mean age of 34.5 years. Forty-one patients had pure mitral stenosis (MS), 18 had predominant mitral stenosis (MSmr), 4 had mitral stenosis and regurgitation approximately of an equal degree (MSMR), and 7 had pure or predominant mitral regurgitation (MR or MRms). One patient had associated systemic arterial hypertension and 17 had associated aortic valvular lesions—pure aortic regurgitation (of different degrees) or combined with aortic stenosis. In all patients the clinical diagnosis of the mitral valve disease was proved by cardiac operation (57 patients), by right cardiac catheterization (12 patients), or by angiocardiography (1 patient). There was a control group

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of 40 normal subjects 19 women and 21 men Their ages ranged from 14 to 54 years with an average age of 28 years

Lead II of the electrocardiogram (ECG) an indirect carotid tracing (CT) from the right carotid artery a left ventricular apex cardiogram (ACG) and a medium frequency phonocardiogram (PCG) at the mitral area were recorded simultaneously with the patient lying in the left lateral decubitus position in apnea at the end of a normal expiration All patients included in the study had typical left ventricular electrocardiographic QRS complexes over the apex beat Pulse wave (linear) condenser microphones (Boucke Brecht) for recording ACG s and CT's and a crystal microphone for recording PCG s were used connected to a direct writing multichannel recorder Hellige Model 9400/6 The records were taken at a paper speed of 50 mm per second

The following time intervals were measured (Figs. 5 and 6) *Initial phase of ventricular contraction or C 1 interval* from the onset of the systolic wave (C point) on the ACG to the onset of the main vibrations of the first mitral sound in the PCG *rapid filling wave or O F interval* from the O point to the F point on the ACG *transformation time or Q 1 interval* from the onset of the QRS complex to the onset of the main vibrations of the first mitral sound *isovolumic relaxation or 2A OS interval* from the onset of the high frequency vibrations corresponding to the closure of the aortic valve to the onset of the first vibration of the opening snap

The following indices and formula were calculated (*C* 1) – (*O F*) (*Q*-1) – (2*A*-*OS*) or Wells index[3] (1954) $\left(\frac{Z+V}{2}\right) = 231/$ (*Q*-1) – (2*A*-*OS*)/ + 17 4 or Davies formula[4] (1967) The (*C* 1) – (*O*-*F*) index was obtained on the basis of hundredths of a second

In calculating the Wells index the Q-1 and 2A-OS intervals measured were corrected to a standard heart rate of 75 per minute (R R interval = 800 msec) using the Ježek[5] (1961) formulas $Q\ 1_{800} = y_x\ x$ – 0 04(800 – *R R*) and $2A\text{-}OS_{800} = y_x\ x +$ 0 06(800 – *R R*) where $y_x\ x$ is the measured value and *R R* the duration of the preceding cardiac cycle In calculating the Davies formula the uncorrected values of these intervals were used The C 1 interval because of its shortness was not corrected. The O F interval does not need any correction since in MS the length of the preceding cardiac cycle does not influence its duration[2]

For all measurements a minimum of three consecutive cycles was used Where there was atrial fibrillation three (rarely less) separate cycles of approximately 800 msec duration were chosen

Standard statistical methods for evaluation of the significance of the results were employed

Results

The results are shown in Table I The results obtained by Wells and Davies methods are given for the purpose of comparison All methods were employed in the same groups of patients. All patients had an opening snap in the PCG except four in the group with pure or predominant MR In these cases the period of isovolumic relaxation was measured by the use of the ACG (2A-O interval)[6] Naturally in the normal subjects this same period was also measured by the use of the ACG According to data given in literature in persons without significant MS the O point coincides closely with the crossing of left ventricular and left atrial pressure curves and the opening snap respectively[7]

(C 1) – (O-F) index In patients with MS or MSmr with a diameter of the mitral orifice of 15 mm or less, the values of the (C 1) – (O F) index varied between –2 and +6 5 the mean value in the patients with MS (+3 12 ± 2 36) being higher than that in the patients with MSmr (+1 83 ± 2 27 $p < 0.05$) Only one patient (with MS diameter of mitral orifice 15 mm) had –2 (Fig 1) Both patients with MS with a diameter of the mitral orifice above 15 mm (Group MSIV) had normal values. All the values of the (C 1) – (O-F) index (except one) in the patients with MS and MSmr with a diameter of the mitral orifice of 15 mm or less did not overlap those in the normal subjects and the patients with MR(ms) There was a good correlation between the (C 1) – (O F) index and the

Table I. Results obtained by means of (C-I) − (O-F) index, Wells' index, and Davies' formula

Groups	No. of cases	(C-I) − (O-F) index			Wells' index			Davies' formula		
		Range	Mean	S.D.	Range	Mean	S.D.	Range	Mean	S.D.
Normal subjects	40	−7.0 to −2.0	−4.05	±1.36	−7.0 to −1.0	−4.125	±1.84	1.23 to 15.09	7.86	±3.53
MS total	41	−3.0 to +6.5	+2.12	±2.38	−4.5 to +3.0	−0.51	±1.83	8.16 to 24.33	16.24	±4.48
	(33)	(−3.0 to +6.5)	(+3.03)	(±2.51)	(−4.5 to +2.6)	(−0.40)	(±1.99)	(8.16 to 24.33)	(16.56)	(±4.51)
MSI*	16	+1.5 to +6.5	+4.25	±1.48	−3.0 to +2.4	−0.31	±1.60	10.47 to 24.33	17.18	±4.35
MSII†	17	−0.5 to +6.0	+2.56	±1.83	−3.0 to +2.6	−0.45	±1.58	10.47 to 23.17	16.53	±3.79
MSIII‡	6	−2.0 to +3.0	+0.75	±2.04	−3.0 to +3.0	−0.43	±2.38	8.16 to 21.33	14.31	±3.81
MSIV§	2	−3.0 to −2.5	−2.75	±0.36	−4.5 to −1.5	−3.0	±2.12	9.31 to 12.93	11.83	±3.36
MSmr	11	1.0 to +6.0	+1.83	±2.27	−8.0 to +2.0	−1.41	±2.83	−1.06 to 24.33	14.30	±5.68
	(10)	(−1.0 to +6.0)	(+2.12)	(±2.43)	(−5.3 to +2.0)	(−1.08)	(±2.15)	(5.85 to 24.33)	(15.18)	(±5.16)
MSMR	4	−2.0 to +0.5	−1.12	±1.18	−3.1 to −0.5	−1.80	±1.19	10.47 to 15.09	13.65	±2.17
	(3)	(−2.0 to +0.5)	(−1.17)	(±1.44)	(−2.3 to −0.5)	(−1.37)	(±1.01)	(13.93 to 15.09)	(14.70)	(±0.69)
MR(ms)	7	−13.0 to −3.0	−5.43	±4.27	−6.0 to +0.5	−2.04	±2.30	8.16 to 19.71	14.76	±3.85
	(4)	(−15.0 to −3.0)	(−6.75)	(±5.56)	(−5.0 to −0.5)	(−2.45)	(±2.35)	(8.16 to 19.71)	(13.90)	(±4.79)

The values in parentheses refer to the patients without systemic arterial hypertension and aortic regurgitation.
*MSI: Diameter of mitral orifice 2 to 5 mm.
†MSII: Diameter of mitral orifice 5.5 [illegible] mm.
‡MSIII: Diameter of mitral orifice 11 to [illegible] mm.
§MSIV: Diameter of mitral orifice above [illegible] mm.

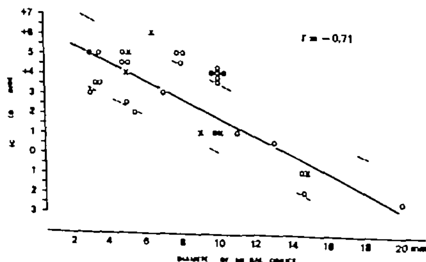


Fig. 1. The relationship of the (C-I) − (O-F) index to the diameter of mitral orifice (52 patients: 41 with MS (O) and 11 with MSmr ( )). The correlation coefficient, the calculated regression line, and the standard deviation from regression are shown.

long diameter of the mitral orifice in MS and MSmr (correlation coefficient r = −0 71) (Fig 1) The values in the patients with MSMR lay between those of the patients with MS(mr) and MR(ms) and had less diagnostic significance.

Wells index and Davies formula The results obtained by the use of these methods in the same patients groups also differed considerably from those in the normal subjects (p <0 05 to <0 001) Only the values in the patients with MS with a diameter of the mitral orifice above 15 *mm* (Group MSIV) were quite close to those in the normal subjects (p <0 50 and <0 25 respectively Tables I and II) But the values of the patients did not differ essentially with respect to the kind of mitral valve disease and overlapped each other to a great extent (Table I) The differences of the mean values between the various patients groups examined using Wells and Davies methods, were not significant (Table II) No linear relation can be discerned between the

Table II (C I) — (O-F) index Wells index and Davies formula Statistical data for the reliability of differences between the various groups examined

Groups	(C I) — (O-F) index		Wells index		Davies formula	
	t	p	t	p	t	p
MS and NS	16 18	<0 001	13 59	<0 001	9 09	<0 001
	(14 10)	(<0 001)	(8 39)	(<0 001)	(8 77)	(<0 001)
MSI and NS	18 71	<0 001	7 71	<0 001	7 58	<0 001
MSII and NS	16 33	<0 001	6 79	<0 001	7 86	<0 001
MSIII and NS	5 49	<0 001	3 65	<0 001	2 72	<0 01
MSIV and NS	1 54	<0 25	0 74	<0 50	1 58	<0 25
MSmr and NS	9 98	<0 001	4 09	<0 001	4 38	<0 001
	(8 30)	(<0 001)	(4 50)	(<0 001)	(4 53)	(<0 001)
MSMR and NS	4 58	<0 001	3 51	<0 001	4 66	<0 001
	(3 32)	(<0 001)	(4 22)	(<0 001)	(9 42)	(<0 001)
MR(ms) and NS	0 84	<0 50	2 28	<0 05	4 39	<0 001
	(0 97)	(<0 50)	(1 46)	(<0 25)	(2 46)	(<0 02)
MSI and MSII	1 33	<0 25	0 23	>0 50	0 47	>0 50
MSI and MSIII	3 85	=0 001	0 10	>0 50	1 03	<0 50
MSI and MSIV	7 92	<0 001	1 74	<0 25	2 19	<0 05
MSII and MSIII	3 03	<0 01	0 03	>0 50	0 79	<0 50
MSII and MSIV	7 01	<0 001	1 64	<0 25	1 98	<0 10
MSIII and MSIV	3 09	<0 05	1 45	<0 25	0 87	<0 50
MS and MSmr	1 98	<0 05	1 35	<0 25	1 29	<0 25
	(1 10)	(<0 50)	(0 81)	(<0 50)	(0 84)	(<0 50)
MS and MSMR	6 10	<0 001	1 94	<0 10	2 01	<0 05
	(4 47)	(<0 001)	(1 36)	(<0 25)	(2 11)	(<0 05)
MS and MR(ms)	5 17	<0 001	1 67	<0 10	0 92	<0 50
	(3 47)	(<0 001)	(1 68)	(<0 10)	(1 04)	(<0 50)
MSI and MR(ms)	5 86	<0 001	1 81	<0 10	1 34	<0 25
MSII and MR(ms)	5 41	<0 001	1 62	<0 25	1 03	<0 50
MSIII and MR(ms)	3 36	<0 01	1 24	<0 25	0 09	>0 50
MSIV and MR(ms)	1 48	<0 25	0 56	>0 50	1 16	<0 50
MSmr and MSMR	3 70	<0 002	0 46	>0 50	0 38	>0 50
	(3 03)	(<0 01)	(0 40)	(>0 50)	(0 29)	(>0 50)
MSmr and MR(ms)	4 27	<0 001	0 59	>0 50	0 23	>0 50
	(3 09)	(<0 01)	(1 08)	(<0 50)	(0 43)	(>0 50)
MSMR and MR(ms)	2 50	<0 05	0 23	>0 50	0 61	>0 50
	(1 92)	(<0 25)	(0 83)	(<0 50)	(0 32)	(>0 50)

NS = Normal subjects.
The values in parentheses refer to the patients without systemic arterial hypertension and aortic regurgitation.

values of the Wells index and the long diameter of the mitral orifice in MS and MSmr (r = 0 06) The significance of the differences of the mean values obtained by the use of Wells and Davies methods did not become essentially greater when the patients with elevated systemic arterial pressure and aortic regurgitation [3] were excluded (Table II)

In a series of 11 patients with MS and MSmr examined before mitral commissurotomy and two to three weeks later the preoperative and postoperative values did not overlap when using the (C 1) − (O-F) index while these values obtained by the Wells method overlapped each other in 45 45 per cent (Fig 2)

Discussion

The (C 1) − (O-F) index is based on time intervals that are closely related to the degree of mitral stenosis.

C 1 interval The delay in the first mitral sound is a characteristic sign of MS. This phenomenon is due to increased left atrial pressure, delayed rise in left ventricular pressure (especially after a short diastole) and rigid mitral cusps.[3] The delayed rise in left ventricular pressure is most likely related to diminution of the left ventricular diastolic volume. [9] The delayed first mitral sound is usually assessed by the Q-1 interval (or transformation time) This period comprises the electromechanical interval and the initial phase of ventricular contraction (before the atrioventricular valves close) The electromechanical delay is represented by the time interval between the onset of the QRS complex and the onset of the systolic wave on the ACG (C point) The electromechanical interval (or Q-C interval) varies considerably but not in relation to the kind of the mitral valve disease.[1] That is why it often modifies the results in assessing the delay of the first mitral sound and diminishes the diagnostic value of transformation time. By the use of the ACG it is possible for the electromechanical interval to be excluded and the actual delay in the first mitral sound determined There was a significant correlation between the duration of the C 1 interval and the long diameter of the mitral orifice (r = −0 45) (Fig 3)

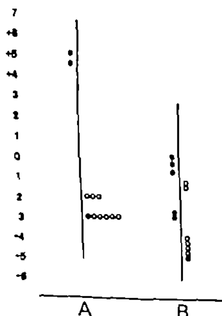


Fig. [illegible] Results obtained in 11 patients with MS and MSmr examined before mitral commissurotomy (●) and [illegible] to three weeks later (O). The pre[illegible] and postop[illegible] values did not overlap when [illegible] the (C 1) − (O-F) index (A) while those values obtained by the Wells method (B) overlapped each other in 45 45 per cent.

O-F interval. This interval diminishes considerably in patients with a diameter of the mitral orifice of 15 mm. or less. In the patients with a diameter between 2 and 10 mm the rapid filling wave was completely absent in 61 1 per cent in MS and in 38.5 per cent in MSmr [9] The duration of the O-F interval correlates well with the valve diameter (r = 0 64) (Fig 4) The alterations of the rapid filling wave in MS are characteristic and refer not only to its duration and amplitude but to the timing of the O point as well. Recently there has been evidence that the O point in MS does not correlate as well with the crossing of left ventricular and left atrial pressures as does the mitral opening snap.[7,13] In severe MS the 0 point generally follows this crossing point by a greater interval than when MS is mild.[7] Therefore, in timing the rapid filling phase the opening snap cannot replace the 0 point. The 0 point identifies the beginning of ventricular filling and does not correspond to the mitral opening itself [14]

long diameter of the mitral orifice in MS and MSmr (correlation coefficient r = −0.71) (Fig. 1). The values in the patients with MSMR lay between those of the patients with MS(mr) and MR(ms) and had less diagnostic significance.

Wells index and Davies formula. The results obtained by the use of these methods in the same patients groups also differed considerably from those in the normal subjects ($p < 0.05$ to < 0.001). Only the values in the patients with MS with a diameter of the mitral orifice above 15 mm (Group MSIV) were quite close to those in the normal subjects ($p < 0.50$ and < 0.25 respectively, Tables I and II). But the values of the patients did not differ essentially with respect to the kind of mitral valve disease and overlapped each other to a great extent (Table I). The differences of the mean values between the various patients groups examined using Wells and Davies methods were not significant (Table II). No linear relation can be discerned between the

Table II. *(C-I) − (O-F) index, Wells index and Davies formula. Statistical data for the reliability of differences between the various groups examined*

Groups	*(C-I) − (O-F) index*		*Wells index*		*Davies' formula*	
	t	*p*	*t*	*p*	*t*	*p*
MS and NS	16.18 (14.10)	<0.001 (<0.001)	13.59 (8.39)	<0.001 (<0.001)	9.09 (8.77)	<0.001 (<0.001)
MSI and NS	18.71	<0.001	7.71	<0.001	7.58	<0.001
MSII and NS	16.33	<0.001	6.79	<0.001	7.86	<0.001
MSIII and NS	5.49	<0.001	3.65	<0.001	2.72	<0.01
MSIV and NS	1.54	<0.25	0.74	<0.50	1.58	<0.25
MSmr and NS	9.98 (8.30)	<0.001 (<0.001)	4.09 (4.50)	<0.001 (<0.001)	4.38 (4.53)	<0.001 (<0.001)
MSMR and NS	4.58 (3.32)	<0.001 (<0.001)	3.51 (4.22)	<0.001 (<0.001)	4.66 (9.42)	<0.001 (<0.001)
MR(ms) and NS	0.84 (0.97)	<0.50 (<0.50)	2.28 (1.46)	<0.05 (<0.25)	4.39 (2.46)	<0.001 (<0.02)
MSI and MSII	1.33	<0.25	0.23	>0.50	0.47	>0.50
MSI and MSIII	3.85	=0.001	0.10	>0.50	1.03	<0.50
MSI and MSIV	7.92	<0.001	1.74	<0.25	2.19	<0.05
MSII and MSIII	3.03	<0.01	0.03	>0.50	0.79	<0.50
MSII and MSIV	7.01	<0.001	1.64	<0.25	1.98	<0.10
MSIII and MSIV	3.09	<0.05	1.45	<0.25	0.87	<0.50
MS and MSmr	1.98 (1.10)	<0.05 (<0.50)	1.35 (0.81)	<0.25 (<0.50)	1.29 (0.84)	<0.25 (<0.50)
MS and MSMR	6.10 (4.47)	<0.001 (<0.001)	1.94 (1.36)	<0.10 (<0.25)	2.01 (2.11)	<0.05 (<0.05)
MS and MR(ms)	5.17 (3.47)	<0.001 (<0.001)	1.67 (1.68)	<0.10 (<0.10)	0.92 (1.04)	<0.50 (<0.50)
MSI and MR(ms)	5.86	<0.001	1.81	<0.10	1.34	<0.25
MSII and MR(ms)	5.41	<0.001	1.62	<0.25	1.03	<0.50
MSIII and MR(ms)	3.36	<0.01	1.24	<0.25	0.09	>0.50
MSIV and MR(ms)	1.48	<0.25	0.56	>0.50	1.16	<0.50
MSmr and MSMR	3.70 (3.03)	<0.002 (<0.01)	0.46 (0.40)	>0.50 (>0.50)	0.38 (0.29)	>0.50 (>0.50)
MSmr and MR(ms)	4.27 (3.09)	<0.001 (<0.01)	0.59 (1.08)	>0.50 (<0.50)	0.23 (0.43)	>0.50 (>0.50)
MSMR and MR(ms)	2.50 (1.92)	<0.05 (<0.25)	0.23 (0.83)	>0.50 (<0.50)	0.61 (0.32)	>0.50 (>0.50)

NS = Normal subjects.
The values in parentheses refer to the patients without systemic arterial hypertension and aortic regurgitation.

It is difficult to explain the delay of the 0 point in regard to the opening snap in MS. Most likely it is due to the anatomic and functional changes of the mitral valve. These same changes influence the blood flow through the mitral orifice (its rate volume, etc.) In all likelihood the altered blood flow is the main cause for shortening or absence of the rapid filling wave in MS though other factors cannot be excluded (volume of residual blood in the ventricle at the end of systole length of the chordae and myocardial distensibility[7])

It is of practical importance that the length of the preceding cardiac cycle and the presence of aortic insufficiency do not alter conspicuously the duration of the O-F interval in MS.[2,15]

(C 1) − (O-F) index The difference between the C 1 and O-F intervals is a more reliable index to the severity of MS (correlation coefficient r = −0 71) than these two intervals when used independently (= −0.45 and 0 64 respectively) Values of −1 and greater for the (C 1) − (O-F) index suggest severe MS or MSmr with a diameter of the mitral orifice of 15 mm. or less. In general the greater the index the tighter the stenosis (Table I) According to other authors, [15] in some cases of severe MR there has also been a tendency of shortening the O-F interval. These findings do not diminish the value of the presented index because first of all it is proposed rather for the evaluation of the severity of MS than for the differential diagnosis between MS and MR. Furthermore in MR the O-F interval could rarely reach such small values as in MS. It should also be borne in mind that in severe MR there are other specific changes in the rapid filling wave (amplitude, F wave) that render the calculation of the (C 1) − (O-F) index unnecessary

Comparative study As it has been pointed out the statistical analysis (Table II) proved the (C 1) − (O-F) index to give more correct information than other methods that have also been suggested for evaluation of the severity of MS Significant differences of the mean values were obtained not only between the patients with MS and those with other mitral valvular lesions (MSmr MSMR MR MRms) but

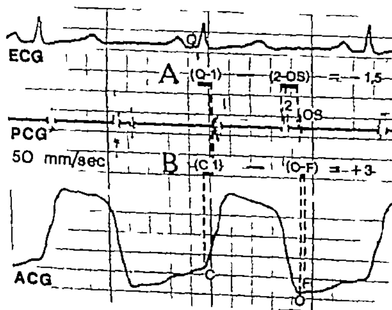


Fig. 5 The result obtained by the use of Wells method (*A*) compared to that of the (C-1) − (O-F) index (*B*) in female patient, age 48, who had severe MS. The valve diameter assessed at operation was 7 mm. The (C 1) − (O-F) index (+3) correlated well with the degree of mitral stenosis, while the Wells index (−1.5) was not indicative of severe MS.

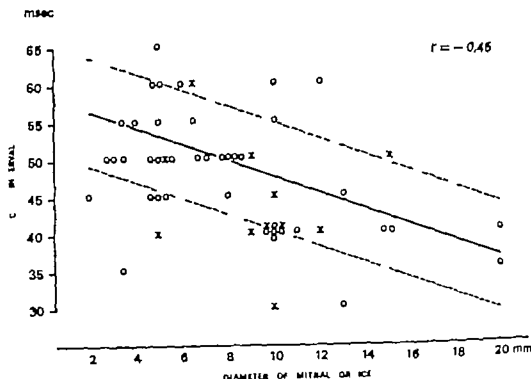


Fig 3 The relationship of the C 1 interval to the diameter of the m tral orifice in 52 patients w th MS (O) and MSmr (x)

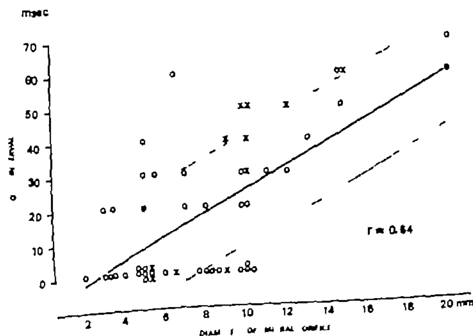


Fig 4 The relationship of the O-F interval to the diameter of the itral orifice in 52 patients with MS (O) and MSmr (x)

stenosis. It is valid in patients with associated valvular lesions as well.

I am indebted to Professor D. Dimitrov, Director of the Department of Cardiac Surgery (Postgraduate Medical School, Sofia), where the patients for the present study underwent operation and catheterization.

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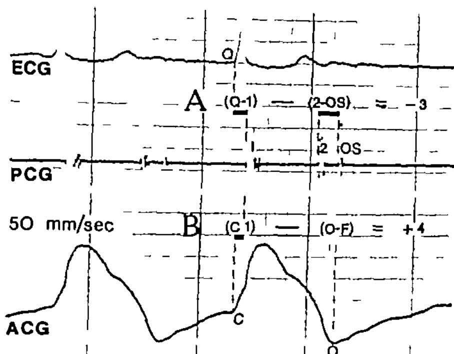


Fig *6* Tracing from a woman age 45 with severe MS The valve diameter assessed at operation was 5 mm. The (C 1) – (O-F) index (+*4*) was characteristic of tight MS while the Wells index (–*3*) was very low

also between the patients with different degrees of MS The difference was not significant between the Groups MSI (diameter of mitral orifice ? to 5 mm) and MSII (diameter 5 5 to 10 mm) only In all likelihood that was due to their hemodynamic similarity However almost all the differences of the mean values between the same patients groups were not significant when using Wells and Davies methods (Table II)

The less precise results obtained by the Wells method may be attributed to different causes. Though the Q-1 interval has an apparent superiority over the 2A-OS interval [18] it includes the electromechanical delay which modifies the results obtained As to the 2A-OS interval there are many factors that influence its duration stroke volume,[18] heart rate [3,16,19,20] ventricular pressure (especially the difference in pressure in the left ventricle between aortic valve closure and mitral valve opening as well as the slope of the fall in pressure during the isovolumic relaxation of the ventricle) [4,19,21] aortic pressure [4,19,20,22] age [23] administration of drugs (norepinephrine [24] digitalis[14]) etc The 2A-OS interval does not disclose a significant correlation with the degree of MS[20] and the mean left atrial pressure [21,24]

According to the results obtained in this study the Davies formula is not superior to the Wells index. It should be also added that the (C 1) – (O F) index does not lose its diagnostic reliability in the presence of associated lesions (Table II) as do the Davies formula[4] and the Wells index to a great extent.

After mitral valvotomy the (C 1) – (O-F) index reliably reflects the acutely induced anatomic and functional changes in the mitral valve

Summary

The difference between the duration of initial phase of ventricular contraction (C 1 interval) and the duration of rapid filling phase (O-F interval) is suggested as a new mechanocardiographic index in evaluation of the severity of mitral stenosis. These time intervals are measured on the basis of apexcardiogram and phonocardiogram The (C 1) – (O F) index gives considerably more correct information than other indirect methods used for the same purpose. A linear relation can be observed between this index and the degree of mitral

stenosis. It is valid in patients with associated valvular lesions as well.

I am indebted to Professor D Dimitrov Director of the Department of Cardiac Surgery (Postgraduate Medical School, Sofia), where the patients for the present study underwent operation and catheterization.

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Hydralazine and methyldopa in thiazide-treated hypertensive patients

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*William R Wilson M D***
Iowa City Iowa

For several years most physicians have supported the concept that vigorous antihypertensive therapy is effective in prolonging the lives of patients with malignant and other accelerated forms of hypertensive vascular disease Recent controlled studies[14,17,19] have indicated its effectiveness in decreasing morbidity and mortality in less severe hypertension These reports emphasize the need for better evaluation of the comparative effectiveness and safety of currently available antihypertensive drugs.

Chlorothiazide and its congeners are effective hypotensive agents in many patients with mild to moderate hypertension Hydralazine and methyldopa are useful hypotensive drugs[9,11,14,16,18] commonly prescribed for hypertensive patients along with the thiazide diuretics when the latter are ineffective when given alone Both drugs have undesirable side effects and rarely produce serious reactions[1,2,4,7,8,10,13,20] Often the choice of the second drug has been arbitrary and sometimes dependent upon regional or individual preferences rather than on the results of sound clinical trials. A thorough search of the American literature failed to disclose any well-controlled comparative studies of the hypotensive effectiveness and short term untoward reactions of hydralazine and methyldopa in thiazide-treated hypertensive patients. Therefore the present trial was designed to study the relative hypotensive effectiveness and side effects of these two commonly used drugs in patients receiving a thiazide diuretic

Methods

The candidates for the trial were selected from the Hypertensive Clinic University Hospitals Iowa City Iowa. Thirty of the original group of 45 candidates qualified for the study The criteria for inclusion in the trial were that the patients had uncomplicated essential hypertension and that their standing diastolic blood pressure averaged 100 mm Hg or greater after 4 weeks of hydrochlorothiazide 25 mg four times daily Criteria for exclusion were those outlined by one of us previously[18] In the current study 15 candidates did not qualify because their diastolic blood pressure was re-

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**Burroughs Wellcome Scholar in Clinical Pharmacology

duced below 100 mm. Hg by hydrochlorothiazide during the initial control period.

The purpose of the study was explained to each candidate and written informed consent was obtained during the initial visit. Each patient had a complete history and a physical examination with emphasis on the cardiovascular and renal systems. Heart rate was counted for 30 seconds, and blood pressure in the right arm was taken immediately and after 5 minutes. The cessation of brachial artery pulse sound was used to denote diastolic pressure. Each patient had a chest roentgenogram and electrocardiogram. Urinary excretion of catecholamines was studied in most cases. Renal function was evaluated by urinalysis, intravenous pyelograms, serum urea nitrogen and serum creatinine levels, and by urine culture. Other tests included hematocrit, white blood cell and differential cell counts, an oral glucose tolerance test, and serum levels of uric acid, glutamic oxaloacetic transaminase, and cholesterol. Each patient was given a hypertensive classification based on a grading system previously described. In this system the severity of the hypertension is graded from I to IV and is estimated from the average value assigned to each of six parameters: arteriosclerotic retinal and hypertensive retinal changes, renal, cerebral, and cardiac function, and basal diastolic blood pressure. Greater weight was given to hypertensive retinal changes and elevation of diastolic blood pressure in determining the assigned grade.

At the end of the one-month screening period, a statistician not otherwise participating in the trial randomly assigned to each patient a code numbered regimen. The allocations were performed randomly in triplets into one of the three treatment groups to ensure equal numbers in each group. All patients took three tablets four times a day. One tablet was hydrochlorothiazide, which each patient took throughout the study. The second tablet was either hydralazine or its placebo, while the third tablet was either methyldopa or its placebo. The tablets looked identical at each dosage level.

One group of 10 patients received hydrochlorothiazide, 25 mg., hydralazine placebo and methyldopa placebo four times daily for 12 weeks. The second group received hydrochlorothiazide, 25 mg., and hydralazine, 25 mg., four times daily for 6 weeks, and 50 mg. four times daily for the next 6 weeks. This group also received methyldopa placebo for 12 weeks. The third group received hydrochlorothiazide, 25 mg., and methyldopa, 250 mg., four times daily for 6 weeks followed by 500 mg. four times daily for the last 6 weeks. This group also received hydralazine placebo for 12 weeks. A sealed code for emergency was kept by a physician not connected with the study. Allowances were made to reduce the dosage of methyldopa, hydralazine, or placebo from the higher to the lower dose level or to discontinue treatment if there was severe orthostatic hypotension. Patients would be regarded as treatment failures if one of the following complications developed during the course of the double-blind phase of the study: (1) cerebrovascular accident, coronary thrombosis, or severe angina pectoris, (2) congestive heart failure not responsive to digitalis, (3) malignant hypertension, or (4) other serious toxic effects. There were no treatment failures.

The patients were evaluated every 2 weeks when they were asked about individual side effects of the drugs under study from a checklist of anticipated side effects. Blood pressures and heart rates were observed and recorded. Mean arterial pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. Before the study, the decision was made to analyze only those supine and standing blood pressure values obtained 5 minutes after the initial observations. Appropriate laboratory tests were performed during the control period and at intervals of 6 weeks so that the results could be related to changes in drug dosages. At the end of the study, the drug regimens were decoded after the data were analyzed by analyses of variance and Tukey's test for multiple comparisons of group means. The criterion for statistical significance was a p value of < 0.05.

Results

Physical and background characteristics. Table I shows the physical and background

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*Vincent S. Vakil, M.D.**
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At the end of the one month screening period, a statistician not otherwise participating in the trial randomly assigned to each patient a code numbered regimen. The allocations were performed randomly in triplets into one of the three treatment groups to ensure equal numbers in each group. All patients took three tablets four times a day. One tablet was hydrochlorothiazide, which each patient took throughout the study. The second tablet was either hydralazine or its placebo, while the third tablet was either methyldopa or its placebo. The tablets looked identical at each dosage level.

One group of 10 patients received hydrochlorothiazide, 25 mg., hydralazine placebo and methyldopa placebo, four times daily for 12 weeks. The second group received hydrochlorothiazide, 25 mg., and hydralazine, 25 mg., four times daily for 6 weeks, and 50 mg. four times daily for the next 6 weeks. This group also received methyldopa placebo for 12 weeks. The third group received hydrochlorothiazide, 25 mg., and methyldopa, 250 mg., four times daily for 6 weeks followed by 500 mg. four times daily for the last 6 weeks. This group also received hydralazine placebo for 12 weeks. A sealed code for emergency was kept by a physician not connected with the study. Allowances were made to reduce the dosage of methyldopa, hydralazine, or placebo from the higher to the lower dose level or to discontinue treatment if there was severe orthostatic hypotension. Patients would be regarded as treatment failures if one of the following complications developed during the course of the double blind phase of the study: (1) cerebrovascular accident, coronary thrombosis, or severe angina pectoris, (2) congestive heart failure not responsive to digitalis, (3) malignant hypertension, or (4) other serious toxic effects. There were no treatment failures.

The patients were evaluated every 2 weeks when they were asked about individual side effects of the drugs under study from a checklist of anticipated side effects. Blood pressures and heart rates were observed and recorded. Mean arterial pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. Before the study the decision was made to analyze only those supine and standing blood pressure values obtained 5 minutes after the initial observations. Appropriate laboratory tests were performed during the control period and at intervals of 6 weeks, so that the results could be related to changes in drug dosages. At the end of the study, the drug regimens were decoded after the data were analyzed by analyses of variance and Tukey's test for multiple comparisons of group means. The criterion for statistical significance was a p value of < 0.05.

Results

Physical and background characteristics. Table I shows the physical and background

Table I Physical and background characteristics of the 3 treatment groups

Characteristics	*Totals*	*Regimen*		
		Hydrochlorothiazide and hydralazine	*Hydrochlorothiazide and methyldopa*	*Hydrochlorothiazide and placebo*
Patients, no	30	10	10	10
Age range (mean)	27–70 (50)	33–65 (48)	41–70 (55)	27 58 (47)
Race				
Caucasian	29	10	10	9
Nonwhite	1	0	0	1
Sex				
Male	21	9	6	6
Female	9	1	4	4
Average weight lb	167	172	172	156
Average hypertensive classification	II	II	II	II
Parents or sibling or both, with cardiovascular disease				
None	43	16	14	13
Hypertension	28	5	13	10
Cardiovascular	1	1	0	0
Previous hypotensive drugs				
None	2	0	1	1
Reserpine	3	2	0	1
Thiazides	25	9	8	8
Methyldopa	11	4	1	6
Hydralazine	4	3	0	1
Others	2	0	2	0

*See reference 6.

characteristics of the patients in each group The groups did not differ significantly in average age race distribution body weight or in severity of hypertension About the same number of patients in each group had a positive family history of hypertension or cardiovascular disease There were no appreciable differences in previous hypotensive drug regimens.

The average supine and standing systolic and diastolic arterial pressures and pulse rates at the end of the hydrochlorothiazide control period (Table II) also were similar in the 3 groups. The treatment groups did not differ in control levels of serum urea nitrogen and blood sugar serum creatinine glutamic oxaloacetic transaminase or in hemoglobin levels. A slightly higher control level of serum uric acid (8 4 ± 0 6 mg per 100 ml) in the hydralazine group as compared to those of the other two groups (6 1 ± 0 6 and 5.2 ± 1 0 mg per 100 ml) can be attributed to the slightly greater number of men in that group The placebo group had 4 patients with a positive diabetic glucose tolerance test while the hydralazine group had 6 and the methyldopa group had 2 patients with positive tests

Comparative effects of the three combinations of hypotensive drugs

INTRAGROUP COMPARISONS Table II shows the average supine and standing systolic and diastolic arterial blood pressure and heart rates in each treatment group at the end of the hydrochlorothiazide control period and after 6 and 12 weeks of treatment.

The average supine and standing systolic and diastolic arterial pressures of the 10 patients receiving hydralazine decreased significantly over the 12 weeks. The average heart rate was unaffected by hydralazine The combination of methyldopa and hydro-

Table II Effects of treatments in 30 hypertensive patients

Treatment	No. of patients	Supine pressures		Standing pressures		Heart rate	
		Systolic (mm. Hg)	Diastolic (mm. Hg)	Systolic (mm. Hg)	Diastolic (mm. Hg)	Supine (beats per minute)	Standing (beats per minute)
A. Hydralazine and hydrochlorothiazide	10						
Control*		170 ± 4	110 ± 4	160 ± 8	112 ± 4	73 ± 4	86 ± 5
6 weeks (lower dose)†		157 ± 6	99 ± 5	150 ± 8	97 ± 3	77 ± 3	87 ± 6
12 weeks (higher dose)‡		144 ± 5	92 ± 4	137 ± 6	93 ± 5	77 ± 5	87 ± 5
Probability		<0.01	<0.01	<0.01	<0.01	N.S.	N.S.
B. Methyldopa and hydrochlorothiazide	10						
Control		170 ± 10	110 ± 3	178 ± 12	112 ± 5	80 ± 4	89 ± 3
6 weeks (lower dose)		163 ± 12	98 ± 4	163 ± 15	100 ± 6	80 ± 4	92 ± 4
12 weeks (higher dose)		158 ± 12	92 ± 4	152 ± 13	95 ± 5	74 ± 4	83 ± 3
Probability		<0.01	<0.01	<0.01	<0.01	N.S.	<0.05
C. Placebo and hydrochlorothiazide	10						
Control		168 ± 6	107 ± 2	144 ± 3	109 ± 2	83 ± 4	94 ± 4
6 weeks (lower dose)		159 ± 6	102 ± 4	138 ± 6	104 ± 5	82 ± 3	92 ± 4
12 weeks (higher dose)		163 ± 7	98 ± 3	131 ± 9	105 ± 3	81 ± 5	93 ± 5
Probability		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

N.S. indicates that the changes are not significant at the 5 per cent level.
*Control values represent averages (± S.E.) of last 2 weeks of the hydrochlorothiazide control period.
†Mean values (± S.E.) obtained after 6 weeks of treatment with hydralazine, methyldopa or placebo, respectively, lower dose and hydrochlorothiazide.
‡Mean values (± S.E.) obtained after 12 weeks of treatment with hydralazine, methyldopa or placebo, respectively, higher dose and hydrochlorothiazide.

chlorothiazide also produced significant lowering of supine and standing systolic and diastolic arterial pressures. The average supine heart rate after the two dose levels of methyldopa was not appreciably different from that of the control period. The average standing heart rate after the larger dose level of methyldopa, however, was significantly lower than that of the control period. The changes in supine and standing systolic and diastolic arterial pressures and in heart rates in the 10 patients who received placebo and hydrochlorothiazide were small and not appreciably different from those of the hydrochlorothiazide control period ($p > 0.05$).

INTERGROUP COMPARISONS. The individual changes in supine and standing mean arterial pressures of the patient receiving hydralazine and those of the patients receiving methyldopa are presented in Fig. 1.

ARTERIAL PRESSURE. The reductions in supine mean arterial pressure after hydralazine and after methyldopa were dose-related and greater than those observed with placebo. The hypotensive effects of the two dose levels of hydralazine, however, were similar to those of methyldopa. The patients who had hydralazine or methyldopa as part of their treatment regimen had dose-related reductions in standing mean arterial pressure. The reductions were significantly greater than those of the patients who received placebo and hydrochlorothiazide. The decreases in standing mean arterial pressure after hydralazine, however, were similar to those observed with methyldopa.

HEART RATE. The patients who received hydralazine showed an average small, but insignificant, rise in heart rate in the supine and standing positions. The average supine heart rate of the patients receiving methyldopa was not significantly different from that of the control period. The average standing heart rate after the higher dose of methyldopa, however, was lower than that of the control period.

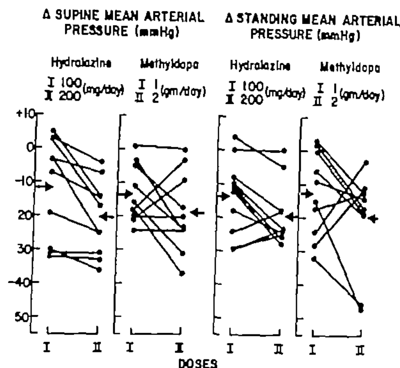


Fig 1 The individual changes in supine and standing mean arterial pressures after two dose levels of hydral[azine] in 10 thiazide-treated hypertensive patients are compared with those of methyldopa in 10 other thiazide-treated hypertensive patients. Arrows indicate average values.

LABORATORY TESTS The addition of hydralazine methyldopa and placebo to the treatment regimen of hydrochlorothiazide alone produced no significant alterations in average levels of serum urea nitrogen serum uric acid two-hour postprandial blood sugar serum creatinine serum glutamic oxaloacetic transaminase and hemoglobin over the 12 weeks.

MINOR UNWANTED REACTIONS TO THE THREE REGIMENS Each patient who entered the 12 week double blind trial completed the study In general the different side effects or unwanted reactions were noted by the same patients and were not reactions which one could attribute definitively to a particular drug None of the symptoms was serious enough to warrant reduction in dosage or stopping treatment None required additional drugs for symptomatic relief The incidence of unwanted reactions in each group is given in Table III

The major central nervous system complaint was nervousness. Other symptoms which were noted to a lesser extent included dizziness, headache blurred vision sleepiness, weakness, and insomnia. The patients who received hydrochlorothiazide and placebo had more of these complaints during the hydrochlorothiazide control period than did the patients in the other two groups. These symptoms diminished as the study progressed over the 12 weeks Vague chest pains and mild shortness of breath also were frequent complaints The incidence of these complaints and their severity however did not increase by the end of the study except in the group receiving hydrochlorothiazide and placebo Impotence the most frequent genitourinary complaint was reported during the control period by 3 patients who subsequently received hydralazine and hydrochlorothiazide Its incidence was not affected by hydralazine Mild nocturia was the other genitourinary complaint noted by one patient receiving hydralazine and by one patient in the placebo group Arthritic symptoms were reported by 4 patients in the placebo group and by none in the other two groups during the hydrochlorothiazide control period None of the patients developed gout lupus erythematosus, hemolytic anemia or positive Coombs tests.

Discussion

The findings in this double-blind study indicate the significant dose-related hypo-

Table III. Untoward reactions in the 3 treatment groups

Treatment	*No. of patients*	*Central nervous system*	*Cardio-vascular system*	*Genitourinary system*	*Musculo-skeletal system*
A. Hydralazine and hydrochlorothiazide	10				
Control		2	0	4	0
6 weeks (lower dose)		1	2	4	0
12 weeks (higher dose)		1	1	4	0
B. Methyldopa and hydrochlorothiazide	10				
Control		3	2	0	0
6 weeks		4	4	0	0
12 weeks		3	2	0	1
C. Placebo and hydrochlorothiazide	10				
Control		14	1	1	4
6 weeks		12	4	2	3
12 weeks		7	4	2	2

*See legend for Table II. The numbers refer to the total number of untoward effects or reactions elicited from or observed in the 10 patients in each treatment group.

tensive effectiveness of hydralazine and methyldopa when used in combination with hydrochlorothiazide. In contrast, the addition of placebo did not alter supine or standing systemic arterial pressures appreciably. The hypotensive effects of hydralazine were similar to those of methyldopa.

Of interest was the observation that one could not determine the drug a given patient was receiving during the double-blind trial by observation of the changes in heart rate. Likewise, one could not predict from the side effects reported what treatment a given patient was taking in the study. Therefore, these results confirm our previously expressed beliefs[4] and those of others[3, 8-11, 13] that comparative double-blind trials are not only feasible, but a necessity in the study of antihypertensive drugs, in order to provide the practicing physician with proper scientific information for the care of his patients.

In this short term study, serious toxic effects were not observed in the patients treated with hydralazine or methyldopa. Neither drug was superior in affording more freedom from minor side effects. The initial enthusiasm for hydralazine has waned over the past 10 years as a result of rather severe toxic effects associated with its long term use in high doses in the treatment of hypertension.[1-] Likewise, occasionally severe toxic effects or unwanted reactions have been reported in patients receiving methyldopa.[1, 23, 24] At dose levels used in this study, however, serious toxic effects are relatively rare. Both drugs are often ineffective antihypertensive agents when used alone, but may be extremely useful when a second drug is necessary in a given hypertensive patient. Since the antihypertensive effectiveness of the two drugs at these dosage levels is approximately equal, the physician may change from one to the other if side effects to the first drug become intolerable to the patient. Finally, caution must be expressed in extrapolation of the findings in these relatively small groups of patients to all populations. Genetic and racial factors may modify the results of a similar study in a different population.

Summary

Thirty hypertensive patients who continued to be hypertensive after one month of treatment with hydrochlorothiazide were allocated at random to one of three treatment groups: hydrochlorothiazide and hydralazine, hydrochlorothiazide and methyldopa, or hydrochlorothiazide and placebo. Baseline measurements of blood pressure and other variables were those obtained after hydrochlorothiazide rather than those after placebo alone or "no treatment." Both hydralazine and methyldopa produced significant dose-related reductions in

supine and standing blood pressures while no appreciable changes were noted in the placebo group The decrements in supine and standing systolic, diastolic and mean arterial pressures with hydralazine and methyldopa were parallel and of equal magnitude. No differences were noted in supine or standing heart rates in the three groups Serious untoward reactions were not observed in this short term study

These studies were supported by grants from the Iowa Heart Association, the National Heart Institute (2T1 HE 5577-08) and by Merck, Sharp and Dohme Division of Merck, Inc., West Point, Pa.
The hydrochlorothiazide and methyldopa used in this study were supplied by E. L. Foltz, M D of Merck & Co. Inc The hydralazine was supplied by William Wagner M D., of Ciba Pharmaceutical Products, Inc., Summit, N J

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Congenital aneurysm of the membranous ventricular septum associated with partial trisomy E syndrome

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Increasing recognition of specific chromosomal abnormalities has resulted in greater awareness of the associated clinical syndromes and accompanying abnormalities of the cardiovascular system. Of these, trisomy E syndrome is frequently accompanied by a variety of congenital cardiac malformations, the most common of which are ventricular septal defect and patent ductus arteriosus.

Congenital aneurysms of the membranous ventricular septum are uncommon cardiac anomalies which have a tendency to be associated with Down's syndrome (trisomy 21). The purpose of this communication is to document the hitherto undescribed association of this type of aneurysm with partial trisomy E syndrome.

Case report

N. L., an African female infant, was born prematurely as the sixth child of a 34-year-old woman. Only the eldest sibling was alive and apparently normal. One sibling exhibited malformations characteristic of trisomy E syndrome and has been the subject of a previous report.

N. L. was admitted to hospital at the age of 4 months because of failure to thrive. She weighed 6 lb., 2 oz. Physical examination revealed a marasmic feeble child with a weak cry, who sucked poorly and was thought to be mentally retarded. Examination of the abdomen, chest, and the cardiovascular and central nervous systems revealed no abnormalities. The following developmental abnormalities were present: the ears were low set, there was marked micrognathia, and the neck was webbed. There was marked limitation of extension of the metacarpophalangeal joints. In addition, the ring and middle fingers of both hands overlapped the index fingers. There was also marked limitation of abduction of the thighs as well as limitation of flexion of the knee and ankle joints. The heels were prominent and projected posteriorly—so-called rocker-bottom heels.

Results of the cytogenetic investigations of peripheral blood culture revealed karyotype 46,XX (partial trisomy E) 46,XX,t(EqBq).

Subsequent course. It was felt that the patient's failure to thrive was related to falling back of the tongue resulting from the severe degree of micrognathia. Despite nasogastric feeding, the child made little progress and died of bronchopneumonia 3 weeks after admission.

Pathological features. The cause of death was viral bronchopneumonia. The other

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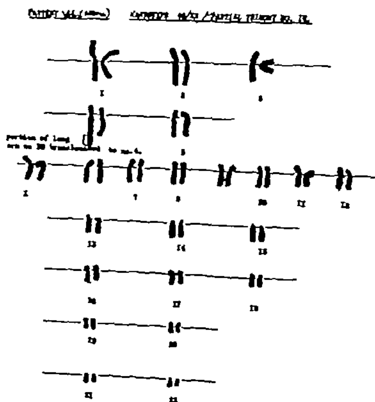
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relevant findings were confined to the heart. The heart arteries and venous connections were normal. From the left ventricular aspect, it was apparent that there was a deficiency in the membranous portion of the ventricular septum (Fig 1 a) The defect was oval 0 75 cm in greatest dimension, and was subjacent to the right third of the posterior cusp and the commissure between the aforementioned and right cusps of the aortic valve.

The defect represented the ostium of an aneurysm of the membranous septum which presented into the outflow tract of the right ventricle (Fig 1 b) The aneurysm was bilocular and 1 cm in greatest dimension and situated immediately inferior to the crista supraventricularis in the region of the papillary muscle of the conus. The tricuspid valve was intrinsically normal, but the anterior leaflet was somewhat distorted by the aneurysmal protuberance The aneurysm was not large enough to obstruct the outflow tract of the right ventricle and its wall was intact.

Cytogenetic studies

Buccal smears were chromatin positive. Peripheral blood was cultured on two occasions and revealed a modal number of 46 with karyotype 46,XX t(Eq+Bq) There was an unmatched long chromosome and a missing No. 4 chromosome (Fig 2) which was previously found in one sibling V L (Fig 3) and in the mother (Fig 4) In the karyotype of the mother a small centric fragment was present and the No 18 chromosome was missing Thus centric fragment was considered to be a deleted number 18 chromosome. As the mother showed no physical abnormality she was diagnosed as a balanced translocation carrier with the long arms of No 18 translocated onto the long arms of No 4 In the propositus this translocation chromosome was inherited from her mother while a normal pair of



...otype of sibling V L 46,XX,t(EqBq)

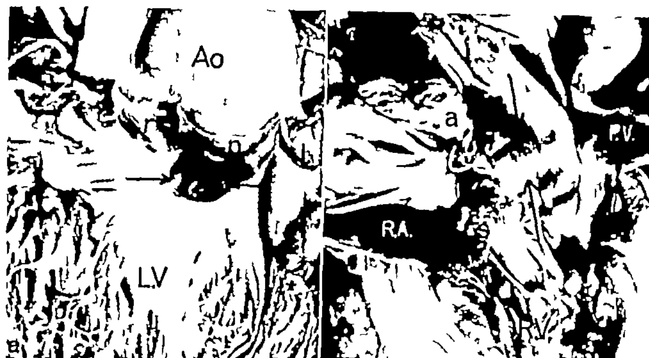


Fig 1 a Outflow tract of left ventricle (*L.V.*) showing ostium of aneurysm of membranous septum (between arrows) *b* Right ventricle (*R.V.*) and right atrium (*R.A.*) showing aneurysm (between arrows) protruding into outflow tract of right ventricle. *P.V.* = Pulmonary valve *a* = anterior and *s* = septal leaflets of tricuspid valve *Ao* = aorta *r p* and *l* = right posterior and left cusps of aortic valve.

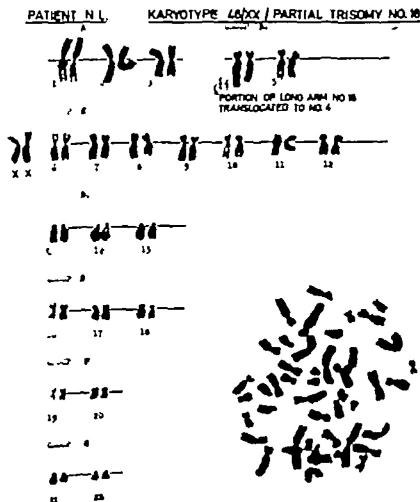


Fig. 2 Karyotype of propositus 46,XX,t(EqBq)

Table I. Results of cytogenetic studies in propositus, sibling, and mother

Subject	Nuclear sex	No. of chromosomes			Total
		45 and less	46		
			Counted	Analyzed	
Propositus	+		15	13: 46,XX,4q+	28
Mother	+	7	8	15: 46,XX,t(18q−4q+)	30
Sibling, V. L.	+	10	5	19: 46,XX,4q+	34

No. 18 chromosomes was present, one from the mother and one from the father. Fig. 5 shows the possible gamete formation and resultant zygote formation. Abnormal zygote formation possibly accounted for the deaths of previous siblings.

Table I gives the results of the chromosome analyses of the propositus and the mother and sibling. The father was not available for chromosome studies.

Discussion

Congenital aneurysms of the membranous ventricular septum are uncommon and their exact pathogenesis obscure. They have a tendency to be associated with a variety of cardiac malformations including aortic insufficiency, membranous subaortic stenosis, coarctation of the aorta, corrected transposition, and atrioventricular canal. In addition, their proximity to the conduction system presumably accounts for the occurrence of arrhythmias and complete atrioventricular block.

Since the membranous septum forms a portion of the floor of the right atrium and also separates the two ventricles, these aneurysms may protrude into the right atrium or right ventricle, and defects in their walls may result in interventricular or left ventricular-right atrial communications.[4] Occasionally, they may be large enough to obstruct the outflow tract of the right ventricle.[11] Frequently, however, as in the case described here, they may be unassociated with any hemodynamic abnormality or arrhythmia when they are imperforate or not large enough to obstruct the outflow tract of the right ventricle.

In the case under discussion with partial trisomy (F), one would expect to find a modified clinical picture of the trisomy E syndrome. The case was referred for cytogenetic studies as a possible trisomy E syndrome. The clinical features of trisomy E were first described by Edwards and associates, and the infant described here manifested all the relevant abnormalities as described above, together with a congenital aneurysm of the membranous ventricular septum. However, her karyotype was 46,XX(partial trisomy E) 46,XX,t(EqBq). Thus we can conclude that the clinical picture in this case is due to trisomy of the long arms of the No. 18 chromosome, and not to trisomy of the whole chromosome 18 (that is both long and short arms). While the association of congenital aneurysm of the membranous septum and Down's syndrome has long been recognized, we would like to add that this condition can occur associated with trisomy of the long arms of the No. 18 chromosome (partial trisomy E).

In a review of 87 autopsied cases of trisomy E, Kurien and Duke[12] found cardiovascular anomalies reported in all but one patient. Ventricular septal defect and patent ductus arteriosus were the commonest associated anomalies, but atrial septal defect, bicuspid aortic and pulmonary valves and the hypoplastic heart syndrome and extensive myocardial fibrosis were found as well; there were no examples

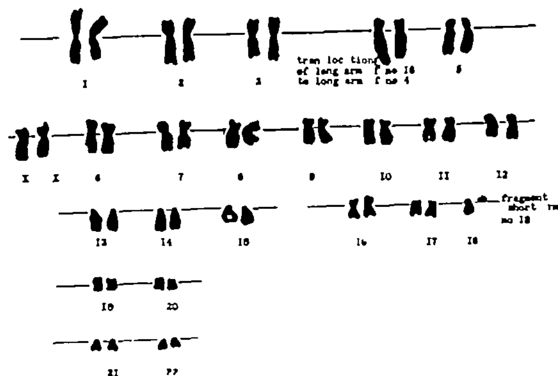


Fig 4 Karyotype of mother of Patients V L. and N L. 46 XX t(EqBq)Eq−

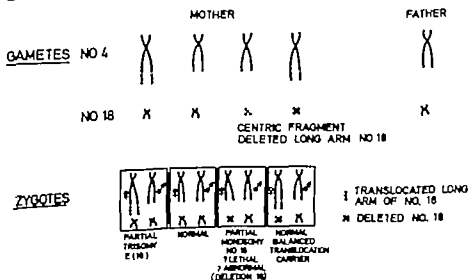


Fig 5 Possible gamete formation with resultant zygotes.

Treatment of recurrent paroxysmal ventricular tachycardia

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Leonard Steinfeld M.D
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New York N Y

Recurrent paroxysmal ventricular tachycardia is generally regarded as a rare condition with ominous prognostic import, and is most often associated with organic heart disease Occasionally it may occur in the pediatric age group and the young adult without underlying heart disease Although generally considered as benign in the younger age groups the prognosis may be variable, with episodes leading to syncope and sudden death Difficulties have been encountered in the management of this arrhythmia. We shall report our experience related to the therapy of a child with recurrent paroxysmal ventricular tachycardia.

Case report

K. T. 10-year-old Negro boy was referred to the Pediatric Service of the Mount Sinai Hospital for evaluation of cardiac arrhythmia noted one month previously during hospitalization for minor surgery in another institution

Physical findings. Physical examination showed well-developed, well-nourished 10-year-old Negro boy who weighed 32 kilos and was 52 inches tall. The pulse was grossly irregular and the rate varied from 80 to 140 beats per minute. Frequent short bursts of tachycardia interrupted the slower rhythm There was no pulse deficit. Peripheral pulses were normal. The blood pressure was 110/70 mm. Hg The thyroid was not enlarged The lungs were clear Cardiac auscultation revealed frequent premature beats and intermittent tachyarrhythmia. The first heart sound was of variable intensity No murmurs or clicks were audible. The liver and spleen were not palpable. The remainder of the physical and neurologic examinations were within normal limits.

Studies and course. An electrocardiogram on admission (Fig. 1) revealed paroxysm of ectopic ventricular beats, preceded and followed by beats of normal sinus origin. QRS complexes in ectopic beats were of broad, bizarre character grossly unlike those complexes associated with beats of sinus origin. During the tachycardia there was a small but noticeable variation in the duration of each bout. A discernible auricular rhythm was demonstrated by the presence of P waves which occurred without relationship to the ectopic QRS complexes. Occasionally ventricular fusion beats were also noted. An esophageal lead and an intracardiac electrogram were recorded to confirm the diagnosis of recurrent paroxysmal ventricular tachycardia.

Hematologic data, protein-bound iodine, serum electrolytes, and urinary vanillylmandelic acid excretion were all within normal limits. An electroencephalogram and an audiogram were also normal.

On the fourth hospital day diphenylhydantoin (Dilantin), 250 mg was given intravenously but did not influence the arrhythmia The next day propranolol, 3 mg. intravenously converted the child to normal sinus rhythm. However when the intra-

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of congenital aneurysms of the membranous septum It is possible however that with increasing awareness of the clinical features of the trisomy E syndrome and the more extensive use of cytogenetic studies the association between the two conditions will be recognized with increasing frequency

Summary

A case of congenital aneurysm of the membranous ventricular septum associated with partial trisomy E syndrome is de scribed The aneurysm was not associated with any hemodynamic abnormality or with any other malformation of the cardiovascular system It is possible that the association of this type of aneurysm with trisomy E will be strengthened in the future since these aneurysms have a tendency to be associated with another variety of chromosomal aberration viz Down s syn drome (trisomy 21)

The authors are indebted to Dr W H Kenny Superintendent, Baragwanath Hospital, and Dr S. Wayburne, Principal Paediatrician, for permission to publish and the Photographic Unit, Medical School University of the Witwatersrand for the illustrations. The authors are also grateful to Professor J Gear Director of the South African Institute for Medical Research for facilities granted to Mrs. N Palmer for technical assistance, and to Mr Max Ulrich for reproduction of karyotypes and tables.

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Treatment of recurrent paroxysmal ventricular tachycardia

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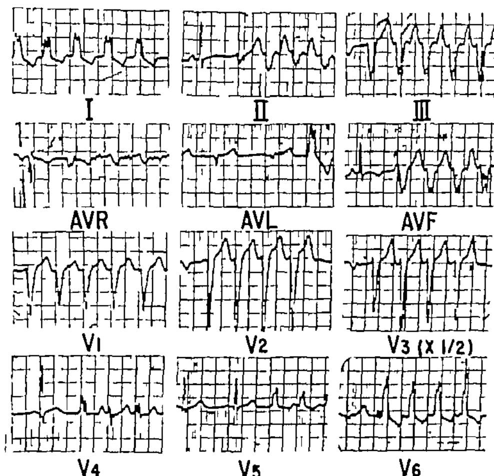


Fig 1 Electrocardiogram of K. T recorded on admission, Nov 28 1967 showed multiple ventricular premature contractions. The ventricular origin of the paroxysm is supported by (1) bizarre widened QRS complexes (2) the differentiation of an independent atrial rhythm at a slower rate (3) identification of partial ventricular capture beats (fusion beats).

venous drip was discontinued the arrhythmia recurred. Oral propranolol therapy was initiated in a dose of 15 mg daily. This was gradually increased to 100 mg. in four divided doses daily which suppressed the ventricular irritability erratically and temporarily. After a trial of two weeks, the original bursts of ventricular tachycardia recurred. Because of the apparent inability of propranolol to adequately suppress ventricular irritability the propranolol was discontinued and the patient was discharged from the hospital.

During the next six months, the patient did not experience any difficulty but two weeks prior to his second admission, he experienced several episodes of chest pain and one of syncope. On admission, recurrent paroxysmal ventricular tachycardia was again demonstrated on the electrocardiogram. Because of the previous failure of propranolol to suppress ventricular irritability a trial of procainamide was attempted. A dose of 250 mg of procainamide was administered orally every four hours and was gradually increased to 750 mg four times daily. This regimen succeeded in suppressing the frequent long runs of ventricular tachycardia and there were no subsequent syncopal episodes, but serial electrocardiograms continued to show some ectopic ventricular activity. Propranolol was therefore added to the procainamide regimen in a dose of 80 mg daily at first and then with graded increments to 160 mg daily. The combination of the two therapeutic agents eliminated the ventricular ectopic beats and converted the child to normal sinus rhythm.

The child was discharged from the hospital, and has been maintained on 750 mg of procainamide and 40 mg of propranolol, four times daily. He has attended the pediatric cardiac clinic during the past 20 months. The recurrent paroxysmal ventricular tachycardia has been completely controlled (Fig 2) and no side effects have been observed from this therapy.

Discussion

In an otherwise healthy child the discovery of isolated ventricular ectopic beats, arising from a single focus, is usually not a cause for concern. Isolated ectopic beats arising from multiple ventricular foci are less likely to be of a benign origin. However prolonged paroxysms of ventricular

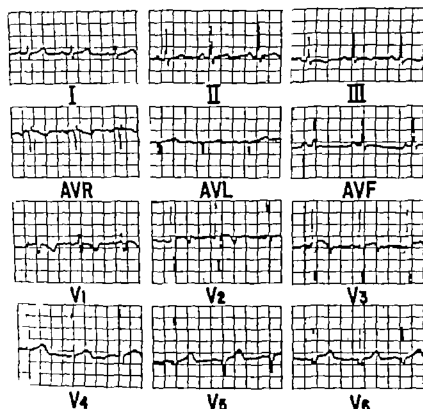


Fig 2 Electrocardiogram recorded on Dec 20 1968, 18 months after administration of procainamide and propranolol N ectopic beats or ther electrocardiographic abnormalities are noted.

tachycardia are generally associated w th serious cardiac disease or intoxication

Recurrent paroxysmal ventricular tachycardia lies between these extremes and prognosis, therefore, is unpredictable. Recurrent paroxysmal ventricular tachycardia is characterized by paroxysmal runs of ectopic beats, interrupted by one or more sinus beats. This pattern may recur over a period of months or years. Although most patients tolerate this arrhyt mia well Bellet has listed several serious complications the threat of sudden death by virtue of spontaneous conversion to ventricular fibrillation anoxia and necrosis in the subendocardial zone of the myocard um nd the development of mural th ombi in the ventricle w th subsequent embolization and infarction. The threat of any one of these complications seems to be adequate reasons for attempting to estore normal sinus rhythm

Recurrent paroxysmal ventricular tachycardia is a challenging therapeutic problem. Past efforts, primarily empirical have failed because the mechanisms responsible for this arrhythmia are undetermined.

A variety of possible etiologic mechanisms have been suggested in patients with recurrent paroxysmal ventricular tachycardia The frequent association of this arrhythmia with exertion emotion and changes in position suggests a mediat ing effect of the autonomic nervous system. Drugs such as atropine sulfate and ergot amine tartrate ha e been reported to ncrease the occurrence of this arrhythmia.

An adequate histologic study of the conducting system in repetitive paroxysmal ventricular tachycardia has not been made. As a consequence of its rarity and prolonged course opportunities for obtaining appropriate tissues are few Congenital and perhaps familial anomalies of the conduction system have been reported.

Parkinson and Papp[4] suggested that a

congenital defect in the conduction mechanism could be an etiologic factor in some of the patients they studied. Paroxysmal ventricular tachycardia has been reported with viral myocarditis. It is possible that some cases of repetitive tachycardia may be due to subclinical viral or other inflammatory disease or the result of chronic myocardial alterations associated with these diseases.[4]

In 1921 Scott employed quinidine to control ventricular tachycardia. Later Armbrust and Levine[6] and others supported the value of this drug. Subsequently procainamide, diphenylhydantoin and potassium chloride have been added to the list of effective therapeutic agents. Most often these agents failed to effect permanent or even prolonged control of the abnormal rhythm.

The success of quinidine and procainamide in controlling some cases of repetitive ventricular tachycardia is probably the result of the effects of these drugs in decreasing the excitability of the ectopic ventricular focus, decreasing the ventricular conduction velocity, prolonging the ventricular refractory period and blocking vagal activity. The effect of diphenylhydantoin presumably lies in its ability to raise resting membrane potential by causing egress of sodium from the cell and influx of potassium similar to its effects on the central nervous system.

Recently the beta-adrenergic blocking drugs have been utilized to control ectopic ventricular tachyarrhythmia with some degree of success. The mechanism of action of these drugs is not entirely clear. However a number of observations have shown that ventricular arrhythmias are enhanced by catecholamines and suppressed by catecholamine antagonists. Although it has been postulated that catecholamine antagonists exert their sole effect by blocking the beta adrenergic receptor, Sekiya and associates[7] demonstrated that the beta adrenergic blocking agent pronethalol also exerts a quinidine-like action. A review of the current literature has revealed that patients with recurrent paroxysmal ventricular tachycardia treated with propranolol (Inderal) do show definite initial improvement as evidenced by either temporary cessation of attacks or a reduction in their duration. The suppressive effect of propranolol however was not maintained in the majority of patients after 8 weeks. To obtain more permanent results, a combination of two or more agents has been proposed.[8,9]

Cohen and associates,[10] recently reported a case of a 15 year-old girl with recurrent paroxysmal ventricular tachycardia successfully treated with a combination of propranolol and electrical stimulation of the left atrium. Zipes and co-workers,[11] reported on a patient whose arrhythmia was converted by a combination of atrial pacing, cardiac sympathetic denervation and propranolol.

The case we described demonstrates the value of propranolol and procainamide in the management of recurrent paroxysmal ventricular tachycardia. The pharmacologic control of recurrent paroxysmal ventricular tachycardia utilizing a single drug including diphenylhydantoin, procainamide and propranolol has not proven to be successful in previous trials. In the case cited the combination of propranolol and procainamide maintained suppression of the arrhythmia without side effects for at least a period of 20 months.

Summary

This case report demonstrates the therapeutic effect of the combination of propranolol and procainamide upon recurrent paroxysmal ventricular tachycardia in a 10-year-old boy. When used as a single agent procainamide, diphenylhydantoin and propranolol proved ineffective in suppressing the arrhythmia. The child has been in normal sinus rhythm for 20 months without side effects, while receiving a combination of propranolol and procainamide. The etiology and therapy of this condition was discussed.

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Silent congenital mitral regurgitation

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Significant mitral regurgitation without an apical systolic murmur has been reported occasionally[1-4] The following is the report of a case of severe silent congenital mitral regurgitation with an unusual presentation

Case report

An 8½-year-old boy was admitted to the Hospital for Sick Children on April 11 1969 following the acute onset of left hemiparesis with left homonymous hemianopia He had been symptom-free prior to this illness and there was no significant past history specifically there was no suggestion of an arrhythmia. A cerebral arteriogram showed an area of avascularity in the right posterior parietal region suggestive of a subdural hematoma. An emergency right occipital craniotomy was performed. No subdural hematoma was found but there was evidence of cerebral edema

In the postoperative period normal sinus rhythm was present. The blood pressure was 100/65 All

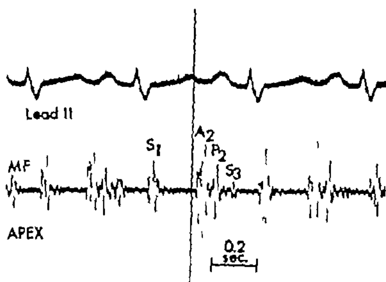


Fig. 1 The phonocardiogram, recorded at the apex shows wide splitting of the second heart sound a prominent third heart sound and absence of murmurs.

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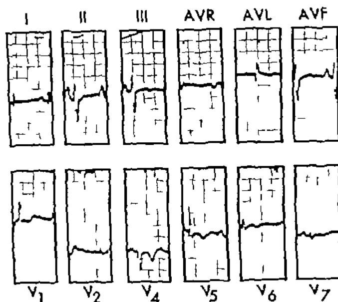


Fig. 2. Electrocardiogram in Patient F. P. two days after craniotomy (April 14, 1969). The "T" waves are inverted or flat in the left ventricular leads. There is evidence of biatrial hypertrophy and right ventricular hypertrophy.

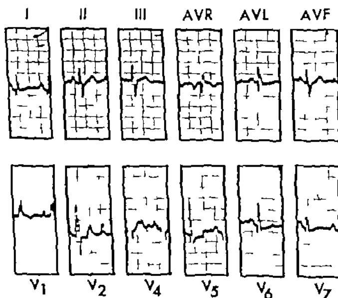


Fig. 3. Electrocardiogram in Patient F. P. six days after craniotomy (April 18, 1969). Although the patient remains on digitalis, the "T" wave changes are reverting to normal.

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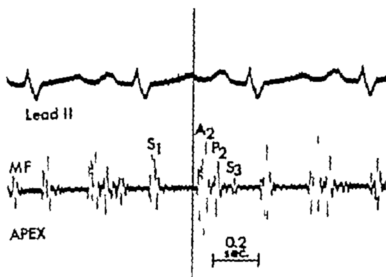


Fig 1 The phonocardiogram, recorded at the apex, shows wide splitting of the second heart sound a prominent third heart sound, and absence of murmurs

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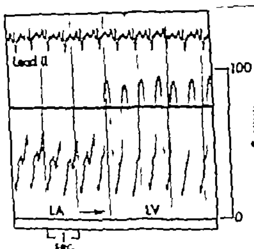


Fig. 6. Pressure tracing obtained during withdrawal of catheter from left atrium to left ventricle. The prominent left atrial V measures 58 mm. Hg. The left ventricular end-diastolic pressure measures 40 mm. Hg.



Fig. 7. Left ventricular cineangiogram in the posteroanterior projection. Contrast outlines the dilated left atrium and the mitral valve ring.



Fig. 8. Portion of excised mitral valve demonstrating the deficient anterior cusp.

formed on April 22, 1969. The left ventricular (LV) end-diastolic and left atrial (LA) pressures were markedly elevated (LV 100/40; LA mean 35 mm. Hg), and there was no evidence of mitral stenosis (Fig. 6). There was marked pulmonary hypertension (MPA) present (MPA 70/35, mean 48 mm. Hg). The mean right atrial pressure was 7 mm. Hg, with an A wave of 12 mm. Hg. There was no evidence of an intracardiac shunt. The cardiac index was 3.7 L. per minute per square meter. Left atrial cineangiography showed gross left atrial enlargement with no filling defects. A left ventricular cineangiogram revealed severe mitral regurgitation with dilatation of the mitral valve ring and probable anterior cusp deficiency (Fig. 7).

On May 26, 1969, successful mitral valve replacement with a 31 mm. diameter Cooley-Bloodwell prosthesis was performed (by Dr. G. Trusler) with

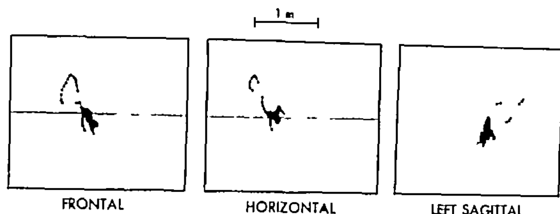


Fig 4 Vectorcardiogram. There is terminal slowing to the right.



Fig 5 Chest x ray *A* Posteroanterior projection *B* Lateral projectio Cardiomeg ly left atrial enlargement, and pulmonary venous congestion are present

peripheral pulses were palpable and of normal quality The jugular venous pressure was elevated 5 cm. above the sternal angle and a prominent A wave was visible in the venous pulse A right ventricular impulse was palpable. On auscultation the first heart sound was accentuated The second heart sound was widely plit b t the splitting varied w th respiration The pul ionary compone t w accentuated A loud third heart sou d w ud ble at the apex. N murmurs were ud ble at ny time and none were recorded phot ocardiog phically (Fig 1)

The electrocardiogram howed sinus rhyth w th a mean frontal QRS axis of 320 degrees a d evidence of right and left atrial hypertrophy and right ventricular hypertrophy The electrocardiogram 2 day after cr niotomy showed T wa e I ersion I Lead V to V (Fig 2) b t f ur days later the T w ves had become positive n these lead (Fig 3) These t ansient T w ve cha ges were thought to be related to his tracranial pathology nd not to dig talis which had been commenced mmediately post per t vely nd co t nued throughout. The ectorcardiogr m showed evidenc of right ventricular hypertrophy w th f gure-of-eight loo the horizontal pla e d terminal forces direct d posteriorly d t the rigl t (F g 4) There so e term nal slow ng all pla es The hest r y howed moder te rdia enlarge ent w th a k d left trial largeme t pul nary enous ngestio , nd Kerley B l nes t both bases (F g 5)

Right nd left heart catheterization was per

Clinical pathologic conference

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Clinical history

A 4?-year-old single Negro male gra edinger was admitted to the Medical College of Virginia Hospital on Jan. 11 1966, because of "burning and stinging" sensations from his aist to his feet accompanied by akness For the past few months he described weakness of the lower extremities and dizziness hen alking p an incline

The patient had apparently been in good health until one year prior to admission hen he first noted the onset of eight loss despite an excellent appetite At this time he bega to pass three to five watery light brown, and occasionally foul-smelling tools daily No melena was noted This usually occurred after eating, and he denied food intolerance.

I March, 1965 he had been admitted to local hospital for investigation of pai in the right testicle ith radiation to both thighs He had become impotent. He denied dysuria or hematuria but tated that he felt giddy Despite xtensi investigation, the etiology of these complaints was not established.

Past medical history as unrevealing H denied venereal disease or previous hospitalizations. He had abstained from alcohol for 5 years A review of systems as noncontributory

Physical examination revealed the following temperature 98.6 F pulse, 82 respirations, 18 blood pressure, 130/74 mm Hg The patient as an obese, middle-aged man ho showed evidence of recent weight loss He as well oriented and coopera tiv but he as illiterat and unable to supply complete history The cranial nerves f nctioned normally fundiscopic examination as nremark able. The heart and lungs ere normal The abdomen as soft and pendulous nd no organs or masses ere detected There as no significant lymphadenopathy The genitalia were normal as was the rectal examination The neurological examination revealed slight weakness of the flexor muscles of both thighs and equally reduced deep tendon reflexes in both lower extremities. No clonus or Babinski reflexes were present. There was a variable sensory loss to both pin prick and cold below the midcervical region.

Laboratory data revealed hemoglobin, 11 Gm. per cent white blood count, 6,700 per cubic millimeter 54 per cent neutrophils, 36 per cent lymphocytes and 8 per cent monocytes. *Platelet count* as 288,000 per cubic millimeter The urine was yellow cloudy and acid ith specific gravity of 1.015. Protein, sugar and acetone were absent. Microscopic examination showed amorphous material, 15 to 25 white blood cells per high-power field and 3 to 5 red blood cells per high-power field. The urine was terile. Blood urea nitrogen was 13 mg. per cent serum creatinine, 1.2 mg. per cent fasting blood sugar 103 mg per cent, 2 hour postprandial blood sugar 113 mg per cent serum sodium, 137 potassium, 4 3 chlorides, 84 and CO_2, 35 mEq. per liter Serum calcium was 10.3 mg. per cent phosphorus, 3.3 mg per cent serum alkaline phosphatase, 0.2 Bessey-Lowry units; serum amylase less than 30 Somogyi units and total bilirubin 0.4 mg per cent with direct reacting fraction of 0.03 mg. per cent Total serum prote was 6.4 Gm. per cent. Protein electrophoresis showed a slight diffuse increase in gamma globulin. Cholesterol, 141 mg per cent, serum iron, 80 mg. per cent total iron-binding capacity 230 mg per cent Venereal Diseases Research Laboratory and Reiter protein complement fixation were nonreactive. Protein-bound iodine as 3.8 mg. per cent, prothrombi

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the use of cardiopulmonary bypass. At operation the mitral valve was grossly incompetent, and there appeared to be deficiency of anterior cusp tissue and *some shortening of the chordae tendineae also* (Fig 8) There was no evidence of a left atrial thrombus.

The immediate postoperative course has been uneventful and clinically the mitral prosthesis is functioning normally *His hemiparesis is markedly* improved with residual weakness of the left hand and fingers only The hemianopia remains. He has been maintained on digoxin and oral diuretics, and long term anticoagulants have been commenced

Discussion

The majority of cases of silent mitral regurgitation previously reported have been rheumatic in etiology and there has often been some degree of mitral stenosis present We are unable to find any other case of silent congenital mitral regurgitation in the literature.

The explanation for the absence of the usual apical systolic murmur has not been established A feature common to the group of cases *reported by Schrire and associates*[1] was marked left atrial enlargement associated with severe mitral regurgitation as in our case The vibrations caused by the regurgitant stream of blood may be damped in a large left atrium with failure of transmission to the chest wall Low cardiac output was not a factor in our case

Summary

A case of silent congenital mitral regurgitation presenting with cerebral embolism is described There was marked deficiency of the anterior mitral cusp The patient has undergone successful mitral *valve replacement*

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sigmoid colon. Oblique views showed posterior displacement of the sigmoid. This was considered to be due to a large tumor mass, possibly a lymphoma. An inferior vena cavagram showed no tumor but later films showed a very large bladder filled with radiopaque material and the cystogram very marked enlargement of a smooth walled bladder. There was leakage of contrast material around the catheter suggesting that the dilation of the bladder was probably neurogenic. The small bowel series was reported as normal and the gastrointestinal series showed minimal deformity of the duodenal bulb.

Cine study of the esophagus and of the small bowel motility was performed. The esophagus showed almost total absence of peristalsis with less severe but significant reduction of small bowel peristalsis as well. A chest x-ray made on the day prior to death shows obliteration of the left hemidiaphragm by a pneumonic process in the lower lobe.

DR. DAVID RICHARDSON. This patient had severely diminished peristalsis of the esophagus, less striking decrease of small bowel motility, a neurogenic bladder and terminal pneumonia and in addition orthostatic hypotension, diarrhea, steatorrhea, urinary retention from a neurogenic bladder, impotence, and absence of sweating. He had questionable evidence of sensory and motor neuropathy as manifested by variable responses to sensory testing and abnormal nerve conduction studies. He did not have diabetes. A normal response to intravenous tolbutamide ruled out diabetes mellitus. He did not have syphilis nor any physical findings suggestive of Parkinson's syndrome. This patient had low urinary excretion of norepinephrine, a finding noted by Luft and von Euler[8] in idiopathic orthostatic hypotension. He thus meets well the criteria for the syndrome of autonomic dysfunction, namely, idiopathic orthostatic hypotension.

On his first admission to the hospital hypochloremia and an elevated blood CO_2 content were present with a normal serum potassium concentration. These findings are consistent with metabolic alkalosis and suggest mild potassium deficiency presumably related to diarrhea. He was treated with urecholine and Lomotil with improvement in bladder function and reduction in diarrhea. The administration of 9-alpha hydrocortisone improved the orthostatic hypotension while in the hospital. At home his diarrhea recurred and he returned to the hospital with pneumonia and hypokalemia, probably the result of diarrhea and steroid therapy. He died of cardiac arrest shortly thereafter, possibly the result of hypokalemia.

The circulatory abnormalities accompanying the erect posture are of special interest. (These are summarized in Table I.)

In idiopathic autonomic dysfunction

Table I. Circulatory response to orthostasis

Normal	*Idiopathic autonomic dysfunction*
1. Pooling of blood below diaphragm, probably in veins	1. Same
2. Shift of blood out of chest	2. Same
3. Fall in right atrial pressure	3. Same
4. Decrease in cardiac volume and output	4. Same
5. Transient fall in arterial pressure	5. Same
6. Stimulation of carotid baroreceptors	6. Fails
(a) Increased heart rate	(a) None
(b) Peripheral arteriolar constriction	(b) Minimal
(c) Mild venoconstriction	(c) None
7. Maintenance of arterial pressure and cerebral blood flow but reduced flow to skin, muscle, kidney, and reduced cardiac output	7. Fall in arterial pressure and cerebral blood flow (fainting)

concentration 70 per cent. Lupus erythematosus preparations were negative on three occasions. The urine was negative for arsenic and only 0.02 mg. of lead was found in a 24 hour specimen. A bone marrow aspiration was normal. Serum B_{12} level was 510 μμg and serum folate 2 to 4 μg.

An electrocardiogram demonstrated nonspecific ST and T wave changes.

X rays of the chest, skull, and small bowel were normal. Films of the pelvis showed narrowing of the joint spaces in the hips and sacro-iliac joints. The cervical, dorsal, and lumbosacral spine films revealed only minimal degenerative changes. Upper gastrointestinal series revealed scarring of the duodenal bulb. Barium enema was unsatisfactory because of the presence of a large, over-distended bladder.

Electromyographic studies were compatible with mild generalized peripheral neuropathy. Lumbar puncture revealed normal spinal fluid pressures. No cells were present. Total spinal fluid protein was 40.3 Gm. per cent and the gamma globulin was increased to 14.5 mg. per cent (normal 1 to 3).

The patient's diarrhea and weight loss continued in the hospital but he remained afebrile. Sigmoidoscopy was essentially normal and rectal biopsy revealed normal mucosa with the presence of ganglion cells in the submucosa. Small bowel biopsy was attempted twice without success. An oral glucose tolerance test showed a fasting blood sugar of 92 mg. per cent, 90 mg. per cent in 30 minutes, 90 in 60 minutes, 83 in 120 minutes, 91 in 180 minutes, 75 in 240 minutes, and 91 mg. per cent in 360 minutes. The D-xylose excretion test showed 2.2 Gm. in 5 hours. Fecal fat was 10.3 Gm. per 24 hours. A tolbutamide test revealed a fasting blood sugar of 87 mg. per cent, in 20 minutes, 70 mg. per cent and in 30 minutes 62 mg. per cent.

Evaluation of his bladder dysfunction revealed 1,250 c.c. of residual urine after voiding. A cystometrogram showed a flat curve with an extremely weak voluntary contraction. The bladder held 1,950 c.c. before voiding. A cystogram demonstrated a large smooth bladder without diverticula. Cystoscopy was normal except for minimal contraction at the bladder neck secondary to mild enlargement of the lateral lobe of the prostate. Intravenous pyelogram was normal. It was necessary for the patient to remain in bed in a semiprone position. On sitting the blood pressure declined to 0/0 with resultant syncope. Tilt table studies which included Valsalva maneuvers and infusions of tyramine and phenoxybenzamine suggested inadequate sympathetic innervation of the blood vessels. Bioassays of the urine for noradrenalin showed 0.2 μg/24 hours (normal 24 to 45). Adrenalin was 7.5 μg per 24 hours (normal 5 to 25). A 5-hydroxy indole acetic acid determination was negative.

At this time the patient was started on diphenoxylate with a striking decrease in the frequency of his stools. Although he had lost 150 pounds from his maximum weight of 300 pounds in December, 1965, he gained 16½ pounds on this medication.

Administration of urecholine resulted in improvement of bladder contractility and a significant reduction in residual urine.

The patient was started on 9-alpha fluorohydrocortisone 1 mg. twice daily. He was discharged on March 19, 1966, and followed in the outpatient clinic until April 18, 1966, when he was readmitted to the hospital because of an increase in diarrhea and incontinence. Examination revealed mild mental confusion, decubiti over the ischial prominences, and edema involving the sacrum and extremities. The muscle tone had diminished from the previous hospitalization. Five hundred cubic centimeters of residual urine was obtained, and a Foley catheter was inserted. The temperature which was normal on the day of admission increased to 101° F. on the second hospital day. A chest film revealed a left lower lobe pneumonia. The blood urea nitrogen 18 mg. per cent, serum sodium 147, serum chloride 104, potassium 1.7, and CO_2 34 mEq. per liter.

The patient developed a cardiac arrest the morning of April 20, 1966, which failed to respond to resuscitative measures.

Clinical discussion

DR. DAVID RICHARDSON: All of this patient's clinical difficulty may be explained by one disease entity, namely, idiopathic autonomic dysfunction. The syndrome was originally described in 1925 by Bradbury and Eggleston[1] under the title of "idiopathic orthostatic hypotension," manifested by marked reduction in arterial pressure with syncope on standing, no increase in heart rate on standing despite the fall in blood pressure, heat intolerance, absence of sweating, impotence, chronic diarrhea, mild anemia, and indefinite evidence of somatic neural dysfunction. More recently this syndrome has been titled "idiopathic autonomic dysfunction" to emphasize *autonomic* sympathetic and parasympathetic involvement. This patient presented with dizziness on walking and marked hypotension without increase in heart rate when tilted upright to 45 degrees. He also had diarrhea with fecal incontinence and malabsorption as evidenced by little rise in blood sugar after ingestion of 50 Gm. of glucose, by reduced urinary excretion of xylose after its ingestion, and by increased fat in his stools. He had marked weight loss and mild anemia, both of which I would attribute to malabsorption. There was also obvious bladder distension. At this point we should see the x rays.

DR. RONALD CALKINS: A chest x ray made on admission was interpreted as normal. A barium enema early in the hospitalization demonstrated overdistension of the

sigmoid colon. Oblique views showed posterior displacement of the sigmoid. This was considered to be due to a large tumor mass, possibly a lymphoma. An inferior vena cavagram showed no tumor but later films showed a very large bladder filled with radiopaque material, and the cystogram very marked enlargement of a smooth walled bladder. There was leakage of contrast material around the catheter suggesting that the dilation of the bladder was probably neurogenic. The small bowel series was reported as normal and the gastrointestinal series showed minimal deformity of the duodenal bulb.

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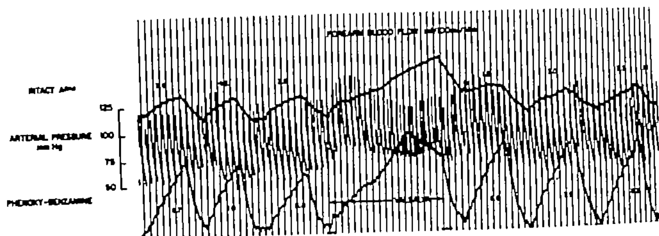


Fig 1 Blood flow in the intact forearm (top tracing), intra-arterial pressure (center), and blood flow in the opposite forearm (lower tracing) in which phenoxybenzamine had previously been administered intra-arterially. Note that following release of the Valsalva maneuver there is decreased blood flow in the intact forearm, but not in the arm in which alpha-adrenergic (vasoconstrictor) receptors had been blocked by phenoxybenzamine. Forearm blood flow, estimated by venous-occlusion plethysmography, is proportional to the slope of the upward-slanting tracings. Actual flow in milliliters per minute per 100 ml of forearm, is indicated by the numbers above the blood flow tracings.

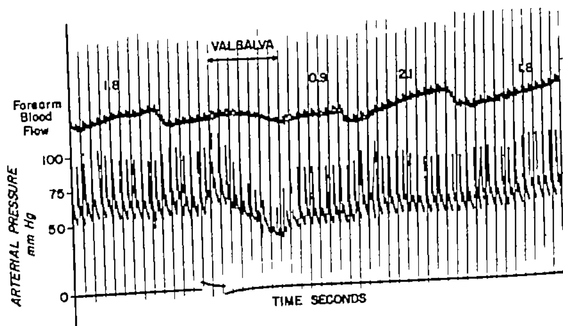


Fig 2 Forearm blood flow above, and intra-arterial blood pressure, below, in M. Q., the patient with autonomic dysfunction. Following release of the Valsalva maneuver there is no overshoot in blood pressure and no reduction in forearm flow, indicating absence of the sympathetic vasoconstriction seen in the healthy subject.

blood pressure falls as a result of failure of the sympathetic nervous system to constrict arterioles upon standing. A number of physiologic and pharmacologic tests also demonstrate impaired function of sympathetic nerves. In healthy people, as shown in Fig 1, there is reduction in forearm blood flow during the overshoot in arterial pressure which follows release of the Valsalva maneuver. This decreased blood flow is mediated by adrenergic nerves, since it is abolished by blockade of alpha adrenergic receptors with intraarterial phenoxybenzamine, as shown in the lower part of Fig 1. It may also be abolished by sympathectomy or by nerve blockade with procaine.[3] In our patient, as shown in Fig 2, no decrease in forearm blood flow after release of the Valsalva maneuver was observed, thus indicating that the

adrenergic nervous system was not functioning properly.

Exact localization of the site of the abnormality of the sympathetic nervous system in idiopathic autonomic dysfunction is not possible. The three major segments of the sympathetic nervous system are (1) *the afferent arc* including carotid and aortic stretch receptors and afferent nerves (2) the central nervous system and (3) the efferent sympathetic nerves. The latter appears to be the most likely site of the difficulty. The following evidence is present to support the conclusion that efferent nerves function abnormally in idiopathic autonomic dysfunction. First, there is low urinary excretion of norepinephrine and low plasma concentration of norepinephrine and this substance is largely manufactured in postganglionic sympathetic nerve endings. Second guanethidine, a drug known to act at efferent, postganglionic sympathetic nerve endings, reproduces the syndrome of orthostatic hypotension without tachycardia. Third the arterial pressure in these patients is hyperresponsive to infused norepinephrine, and hyperresponsiveness to norepinephrine is usually observed after postganglionic sympathectomy.

Thus the circulatory abnormalities in idiopathic autonomic dysfunction probably result from abnormal function of efferent sympathetic neurons supplying heart and systemic arterioles. The functional abnormalities observed in bladder and bowel function, in sweating and in penile erection probably result from dysfunction of both the sympathetic and parasympathetic nerves which innervate these organs. The syndrome can be viewed as peripheral neuropathy largely confined to the autonomic nervous system though in many patients described by others[1-4] as in this case, obvious clinical evidence of somatic neural dysfunction has been observed. According to Schatz Podolsky and Frame, somatic neuropathic signs may precede the orthostatic hypotension by one or two years, and they fail to support the hypothesis that somatic neural dysfunction results from ischemic brain or spinal cord damage secondary to hypotension.

Orthostatic hypotension occurs in a variety of conditions accompanied by reduced blood volume e.g. hemorrhage and adrenal insufficiency. If cardiac adrenergic innervation be intact arterial hypotension will induce tachycardia. Orthostatic hypotension without tachycardia is seen in diabetic neuropathy tabes dorsalis, during guanethidine administration as well as in *idiopathic autonomic dysfunction. Since* our patient had none of the former I must make a diagnosis of idiopathic autonomic dysfunction. I suspect that this syndrome like essential hypertension is the result of a number of various, as yet undiscovered causes. For instance primary amyloid has been noted in one patient in Wagner's series,[7] and Kyle, Kottke and Schirger[8] found 11 patients with orthostatic hypotension among 138 cases of primary systemic amyloid. Rectal biopsy in our patient showed normal mucosa, and I am unable to detect any underlying cause of the autonomic dysfunction in this man.

I suspect that Dr Jones will demonstrate pneumonia in the left lower lobe and the renal and myocardial changes of hypokalemia. I hope she will elucidate the pathology of autonomic dysfunction.

Pathology discussion

DR. MARGARET JONES The heart weighed 500 grams and showed left ventricular hypertrophy and the lungs extensive acute bronchopneumonia in all five lobes. *Staphylococcus aureus* was cultured from the lungs. The kidneys were enlarged 350 grams each and demonstrated *marked cortical* pallor and swelling. The vacuolar degeneration of the tubular epithelium was characteristic of the reversible lesion induced by hypokalemia. This lesion characteristically requires about a week to develop.[9] Changes of low potassium were also present in the myocardium.[9]

We can clarify the pathogenesis of the "idiopathic autonomic dysfunction" in this particular case because it was not idiopathic and due to diffuse amyloidosis. A metachromatic and birefringent substance which stained positively with Congo red infiltrated the autonomic ganglia and nerves as well as the blood vessels of nearly all organs. This substance replaced extensive segments of the muscularis mucosa

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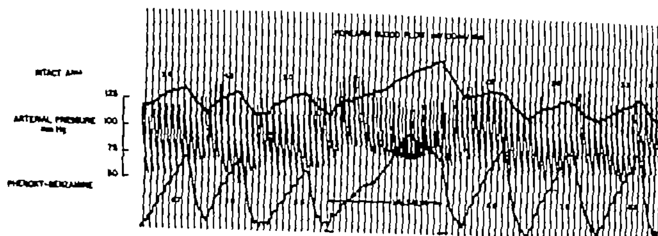


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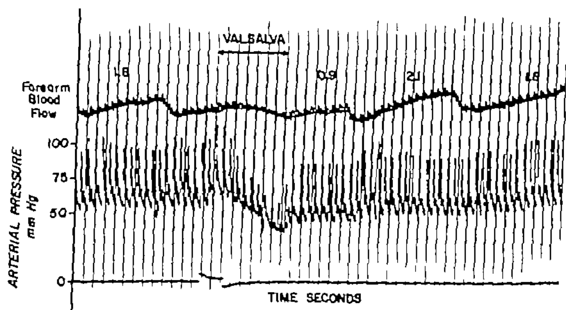


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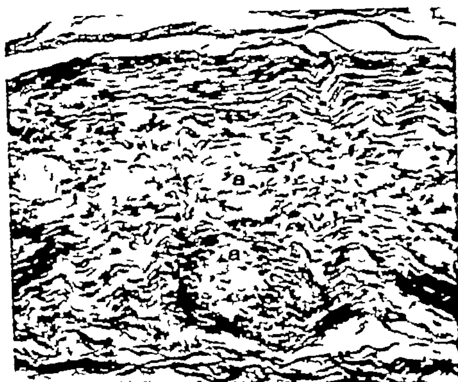


Fig. 4 Amyloid deposits (*a*) distort the architecture of the peripheral nerve. (Hematoxylin and eosin. ×250.)

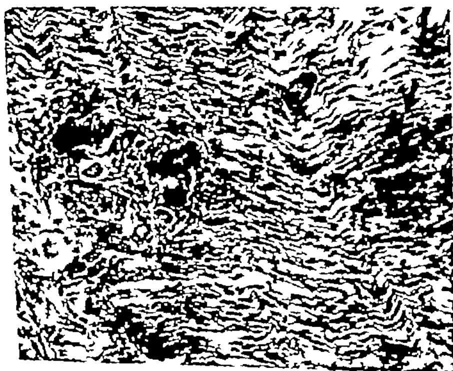


Fig. 5 Section from the margin of a sympathetic ganglion shows deposits of amyloid (arrows) in the walls of capillaries or vasa nervora as well as in the nerve which surrounds the ganglion cells (*G*). (LFB, Periodic acid-Schiff ×250.)



Fig 3 Section of esophagus shows amyloid (arrows) in vessel walls (v) Deposit (arrow) encircle and encroach on the muscular elements (m) as well. I filtration of ne r l elements is not illu trated. (Congo red tain. ×250.)

and also the inner muscular coat of the esophagus (Fig 3) while in the small intestine amyloid deposition was largely confined to the small blood vessels of the submucosa and vasa nervorum In the myocardium extensive amyloid deposits were present around individual muscle fibers. In addition there was focal atrophy and marked vascular involvement with degeneration and loss of myocardial muscle fibers. Amyloid was deposited in rings around individual fat cells in many organs This waxy material spared the brain and upper cervical spinal cord cervical dorsal roots cranial nerves, and meninges. Large segments of peripheral somatic and autonomic nerves were replaced (Fig 4) Sympathetic ganglia were also infiltrated by amyloid (Fig 5) In nerves which showed minimal involvement amyloid deposits were confined to the vasa nervorum Fibrillar material different from that of fibrin or collagen was demonstrated in the capillary basement membrane in muscle (Fig 7) This suggests that amyloid first deposits around the vasa nervora and later gradually replaces large segments of nerve

The central nervous system is not usually involved in symptomatic primary amyloidosis while clinical and pathological evidence of peripheral nervous system involvement probably can be demonstrated in most cases. Investigations of both components are often overlooked Some cases of primary amyloidosis have shown infiltration of the meninges or meningeal vessels with secondary ischemic



Fig. 7. The amyloid deposits (a) are illustrated in subendothelial location of the capillary wall (C). Normal myelinated axons are seen nearby (A). (×7200.) (Electron micrograph courtesy of W. J. S. Still.)

response to noradrenalin infusion in this case, despite the extensive involvement of the vascular bed by amyloid fails to support this generalization.

In regard to the studies of the gastrointestinal tract, it should be emphasized that motility is related not only to intrinsic and extrinsic innervation of the gut, but also to the muscle cells per se.[23] All three modalities as well as the vasculature were altered by the disease process in this patient. Malabsorption in amyloidosis has been reviewed by Herskovic and colleagues, but its pathogenesis in patients with this disease or with diabetic neuropathy is unclear. The precise manner in which factors such as motility affect absorption is unclear. It has been suggested that villous atrophy secondary to ischemia is responsible. There was relatively little atrophy of villi, however, in this case.

In summary, the anatomic diagnoses were (1) amyloidosis involving the peripheral autonomic and somatic nervous system, the heart, gastrointestinal tract, blood vessels, and lipoid tissue; (2) hypokalemic nephropathy and myocardiopathy; (3) acute, purulent bronchopneumonia.

DR. RICHARDSON: Are you saying that all of his symptomatology was the result of amyloid infiltration of nerves and ganglia?

DR. JONES: Yes, although the decreased gut motility was very likely related to amyloid infiltration of the muscle. The malabsorption was probably related to villous atrophy secondary to blood vessel involvement.

DR. JOHN H. MOON: Did the rectal biopsy contain amyloid?

DR. JONES: None was suggested on the initial examination of the surgical section. However, when the diagnosis was known following autopsy, specific stains on recut material from the rectal biopsy showed

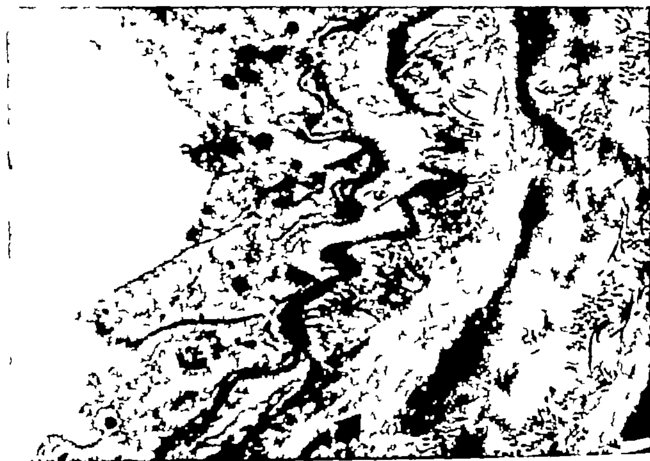


Fig 6 The amyloid fibrils (arrow) which differ from the dense banded collagen fibrils, are illustrated in the wall of a blood vessel (X20 800.) (Electron micrograph courtesy of W J S Still.)

lesions in the brain but the brain is not often primarily involved in widespread amyloidoses. Cerebral amyloidosis an entity noted by Margolis[11] is sometimes associated with deposits in the heart and pancreas in elderly patients. We have preferred to segregate this latter entity from other amyloidoses

Heller and associates[12] suggested that early vascular lesions in amyloidosis were related to reticulin fibers particularly abundant in the basement membrane or to the collagen fibers of the outer media and adventitia He proposed classifying the amyloidoses according to the affinity for reticulin or collagen fibers. Most early lesions with the exception of those involving the peripheral nervous system were of the pericollagenous type However this distinction fails to hold at a structural level The staining reactions and patterns of organ involvement so far described are no longer considered to be satisfactory for classification of the amyloidoses. In all cases so far examined with electron microscopy the fibrillar component of amyloid has been identical[13] Whether all components of the material observed under different circumstances are identical has not been clarified The source of the material or its precursor has not been definitely identified although the fibroblast, the plasma cell and the reticuloendothelial cell have all been implicated

Andrada[14] wrote about 74 patients who presented with impotence sweating defects and gastrointestinal disorders Pathologic examination revealed amyloid deposits in nerves, blood vessels, and gut as observed in this case This is a distinctly unusual constellation of symptoms in non familial primary amyloidosis.[14]

It is of interest that Wagner[7] ruled out amyloidosis as a cause of autonomic dysfunction when hyperresponsiveness to noradrenalin infusion occurred He believed when blood vessels were primarily involved the response could not occur The marked

The effects of acute chloroquine poisoning with special reference to the heart

T A Don Michael M.D., M.R C P (Lond) M R C P (Edin) F A C C
S Atoosazadeh M D
Abadan Iran

Chloroquine was synthesized before World War II and has since become one of the most widely used drugs. It is chemically a 4-amino-quinoline similar to quinidine. Since it was firmly established as a suppressant and prophylactic in malaria, it has been used in the treatment of hepatic amebiasis, in a variety of worm infestations, in cardiac arrhythmias, and in the so-called autoimmune group of disorders. While its toxic effects have been intensively studied and are recognized its precise effects on the heart and circulation in acute poisoning have been poorly documented. This is largely due to its rapidly lethal effect. With the recognition of a growing number of cases of chloroquine poisoning it has become necessary to study its toxicity with respect to the heart and circulation.

This paper outlines the acute cardiotoxic effects of the drug as observed in three humans, and summarizes the findings in five animal experiments.

Case reports

Patient 1 On April 26, 1966, a 17-year-old boy walked into the outpatient department and confessed to having taken 40 tablets of chloroquine (75 mg base each) 1½ hours before. He had been depressed as a result of a skin condition (discoid lupus) for which he had been given the drug. He was swiftly transferred to the ward, where arrangements were made to pump out his stomach. However quite suddenly he began to convulse, and cardiac arrest occurred. In a few minutes, respiration had ceased. External cardiac compression and expired air ventilation were started immediately while an intravenous line and an electrocardiograph monitor were set up. When one of the authors (T. D. M.) first saw the patient, about 15 minutes of closed-chest resuscitation had been administered. The pupils were widely dilated and there was total cardiorespiratory arrest. The electrocardiogram (ECG) however showed a ventricular rhythm with broad QRS complexes (Fig 1 *A*). Ten cubic centimeters of 1:1000 adrenaline hydrochloride and 1 mg of atropine were given simultaneously through the drip. About 5 minutes later the heart started in sinus rhythm and peripheral pulses were felt. In approximately half an hour spontaneous respiration had returned. The electrocardiogram continued to show sinus rhythm (Fig 1 *B*). Expiration however was noticeably labored and secretions were present in the respiratory passages, indicating rigid lungs probably due to pulmonary edema. The pupils gradually constricted and about 6 hours later he responded to pain, and had a positive eyelash-blink reflex. His subsequent course was, unfortunately, progressively downhill. The level of consciousness deteriorated and respiration became irregular. Convulsions and hyperpyrexia developed, the clinical appearance resembling that of a patient with severe head injury or a cerebrovascular accident.

From the Department of Internal Medicine, N I O C Hospital, Abadan, Iran
Abstracted from a lecture given at the Persian Gulf Medical Conference, October 1968.
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*Chief of the Department of Internal Medicine.
**Senior Resident

distinct amyloid in vessel walls. Of course Dr Richardson was misled by the apparent absence of amyloid in the specimen

DR RICHARDSON Did each kidney weigh 350 grams? Why didn't the intravenous pyelogram show large kidneys?

DR CALKINS The intravenous pyelogram was done several months before death Dr Jones indicated the renal pathology was of but a week or two in duration

DR MOON Dr Richardson what else would cause idiopathic autonomic dysfunction?

DR RICHARDSON There are many causes of the syndrome Diabetic neuropathy and guanethidine therapy are among those responsible

DR PAGE HUDSON May idiopathic autonomic dysfunction have an early onset for example in young children?

DR RICHARDSON It is a disease of two groups very young children and middle aged people

DR. JONES What is the treatment of this condition? Do you have any experience with high doses of sodium chloride?

DR RICHARDSON The treatment of this disease includes use of a G suit and induced salt retention Antigravity suits in my experience are troublesome and not very effective Salt retention is fairly effective in relieving orthostatic hypotension It may be induced with desoxycorticosteroid large salt load or 9-alpha fluorohydrocortisone. DOCA and 9 alpha fluoro deplete potassium and this must be prevented I consider 9 alpha fluorohydrocortisone the drug of choice

DR. RICHARD KIRKLAND I had a similar case and made the mistake of giving atropine for abdominal cramps The fever went to 104 and stayed there until we stopped the drug The atropine apparently further enhanced the already inadequate sweating Treatment with DOCA and salt was sufficient to maintain the blood pressure.

DR. DAVID RICHARDSON'S DIAGNOSES (1) idiopathic autonomic dysfunction (2) bronchopneumonia and (3) hypokalemia

FINAL ANATOMICAL DIAGNOSES (1) amyloidosis (primary type) with infiltration of peripheral (autonomic and somatic) nervous system cardiovascular system smooth muscle of gut blood vessels and lipoid tissue (2) bronchopneumonia acute, severe (*Staphylococcus aureus*) and (3) hypokalemia nephropathy and myocardiopathy severe

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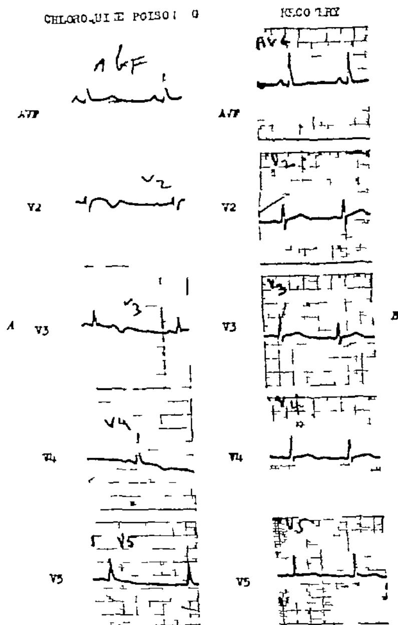


Fig. 2 A. The electrocardiograms illustrate the changes in P tient 3 seen during the phase of hypotension tributed to chloroquine, widening of the QRS complex with decrease of height, and inversion of the T w ve in Leads V V and V with loss of voltage in V There is P pulmonale. B This is contrasted with the normal pattern seen during recovery There is, however no alteration in the P pulmonale.

As a result of these nfortunate occurrences in humans, t was decided to observe the acute cardiovascular effects of chloroquine, administered intravenously in dogs. Since the drug is totally absorbed from the gastrointestinal tract and poorly excreted administration by infusion into a peripheral vein was considered the best method of studying ts effects.

Material and methods

Mongrel dogs were selected examined by a veterinarian, weighed, and anesthetized w th pentobarbital (½ c.c. per kilo-

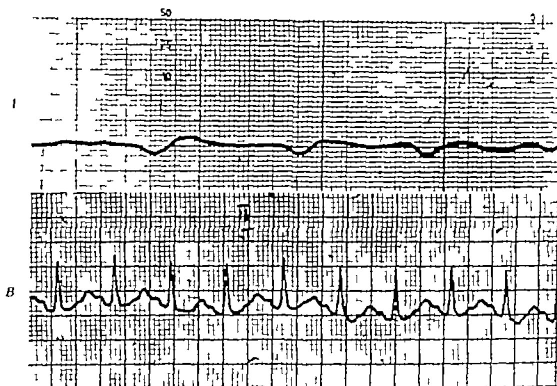


Fig 1 A Ventricular bradycardia with wide QRS complexes seen during cardiac arrest in Patient 1 B Sinus tachycardia seen after resuscitation

Blood transaminase levels were raised Measures to eliminate the poison, combat cerebral edema, and restore the deranged metabolism failed and the patient died four days later An autopsy was refused

COMMENT This case illustrates the rapidity of cardiac arrest caused by chloroquine and the efficacy of adrenaline as a cardiac antidote As far as we know this is the first case reported in which an electrocardiogram was obtained following chloroquine poisoning

Patient 2 A boy of 15 weighing 35 kilograms, was admitted on Aug 29 1966 with a proven diagnosis of benign tertian malaria. He received 600 mg of chloroquine base and 300 mg six hours later His blood pressure at admission was 110/60 A few hours after his second dose, he was discovered drowned in his bath. Cardiorespiratory resuscitation was unsuccessful. A previous routine examination had been negative. An autopsy was not performed.

COMMENT The total dose was within the accepted normal Although the boy could have drowned as a result of a fit there was no previous history of epilepsy It is possible that the patient fainted but in this event the fall of blood pressure could reasonably be attributed to chloroquine. While the evidence for chloroquine toxicity here is indirect and inferred there is sufficient reason to suspect the drug as having led to the death of the patient either by hypotension or by cardiac arrest.

Patient 3 A 59-year-old man was admitted on July 29 1967 with proven tertian malaria. He was an opium addict and had caseocavernous tuberculosis of the right lung, a swollen left leg and rectal prolapse. He had been admitted to another hospital two weeks previously for benign malaria, and was apparently given an unspecified dose of chloroquine and primaquine. On July 31 1967 it was decided to repeat the course of treatment. Six tablets of chloroquine (75 mg base) were given initially and four tablets after six hours. A few hours after the first dose, the pulse dropped from 110 to 50 and the blood pressure from 100/70 to 70/50 The electrocardiogram showed bradycardia with widened QRS and S-T segment depression in V through V and a P pulmonale (Fig 2 A)

The patient showed signs of shock Noradrenaline was administered with no effect. Adrenaline, nikethamide, and hydrocortisone were given and gradual recovery followed. The electrocardiogram following recovery showed a return to normal of the heart rate. QRS duration, S-T segment changes and T waves (Fig 2, B)

COMMENT Pulmonary embolism would be an unlikely alternative as bradycardia was associated with the state of shock The typical electrocardiographic changes and the response to treatment are in line as well as the definite relationship to the administration of chloroquine.

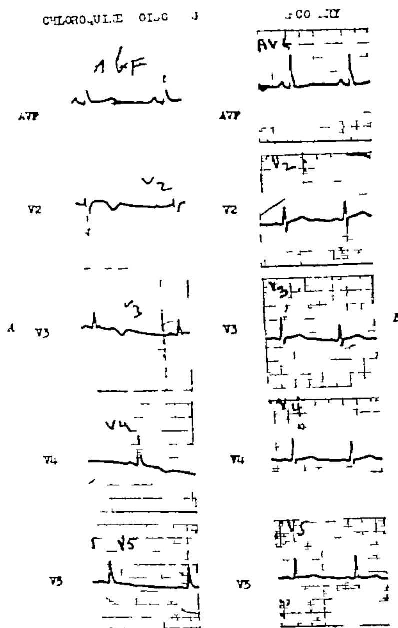


Fig. 2. *A*. The electrocardiograms illustrate the changes in Patient 3 seen during the phase of hypotension attributed to chloroquine, widening of the QRS complex with decrease of height, and inversion of the T in Leads V V and V with loss of voltage in V. There is P pulmonale. *B*. This is contrasted with the normal pattern seen during recovery. There is, however, no alteration in the P pulmonale.

As a result of these unfortunate occurrences in humans, it was decided to observe the acute cardiovascular effects of chloroquine, administered intravenously in dogs. Since the drug is totally absorbed from the gastrointestinal tract and poorly excreted, administration by infusion into a peripheral vein was considered the best method of studying its effects.

Material and methods

Mongrel dogs were selected, examined by a veterinarian, weighed and anesthetized with pentobarbital (½ c.c. per kilo-

gram) A six (standard) lead electrocardiogram was taken using a Phillips two-channel recorder The femoral vein and artery were isolated Central aortic pressures were recorded by cannulating the femoral artery after arteriotomy with a No 8 Cournand catheter This was connected first to a calibrated Statham P 23Db strain-gauge transducer with a saline filled head and then to an electromanometer The latter was linked to the second channel of the recording machine. The left femoral vein was routinely catheterized serving as a route for administering the drug In some experimental animals a unipolar catheter pacemaker (Devices Ltd) was inserted through the opposite femoral vein with an indifferent electrode fixed on the shaven chest wall In two dogs (Nos. 4 and 5) the trachea was intubated and the endotracheal tube connected to a Boyle s machine All catheter manipulations were performed using a portable image intensifier unit. Chloroquine sulfate (Nivaquine) 100 mg per cubic centimeter was injected at the rate of 100 mg of base per minute into a free-running saline drip The dogs were put to death at the end of the experiment

In these experiments the toxic dose is regarded as being the amount at which significant electrocardiographic changes occur while the lethal dose pertains to changes compatible with cardiac arrest

Results

Experiment 1 A 5 kilogram dog was used The changes in the electrocardiogram are summarized in Table I and Graph I After 500 mg of Nivaquine were injected electrical arrest occurred This took the form of QRS complexes which gradually widened and ceased (Fig 3)

Ten cubic centimeters of 1 1 000 adrenaline restored the heart to a ventricular tachycardia which had preceded arrest but did not produce a palpable pulse The toxic dose at which cardiovascular changes were seen was 40 mg per kilogram and the lethal dose of 100 mg per kilogram

Experiment 2 The dog used was 7 5 kilograms in weight After 2 c.c (100 mg) of Nivaquine bradycardia and a loss of QRS voltage, with widening of the complex, occurred (approximately 10 mg per kilogram) After 1 c.c of adrenaline was administered this reverted to 2 1 atrial flutter at a faster rate with taller and narrower QRS complexes (Fig 4)

The drug was then repeated up to a total of 200 mg and the typical agonal changes, seen in the previous experiment were noted Pacing though electrically effective was of no consequence hemodynamically

Experiment 3 The dog used was 18 kilograms in weight. Table II and Graph II illustrate the changes in the electrocardiogram induced by chloroquine while the heart was still in sinus rhythm It was noted that the mean aortic pressure was significant even when the pulse could hardly be felt pointing to failure of the heart as a pump rather than an effect on the peripheral resistance The toxic dose was 18 mg per kilogram and the lethal dose 34 mg per kilogram

Experiment 4 The dog that was used weighed 18 kilograms. This experiment illustrates the evolution of the electrocardiogram with simultaneous data obtained from the indwelling aortic catheter which recorded the pressure pulse during the administration of increasing doses of chloroquine (Fig 5)

Corresponding with Fig 5 the sequential changes seen were as follows

Control The ECG and aortic pressure pulse prior to chloroquine administration is indicated

A The QRS height increases and the aortic pressure rises.

B The QRS height and blood pressure return to the resting state

C The QRS height decreases as its width increases and the aortic pressure begins to fall

D These changes become progressively more marked

E The changes described in the QRS complex become more marked in addition the T wave becomes taller The pressure continues to fall

F The ECG is bizarre with summation of broadened T and P waves. The isoelectric line is lost. The aortic pulse pressure is markedly decreased

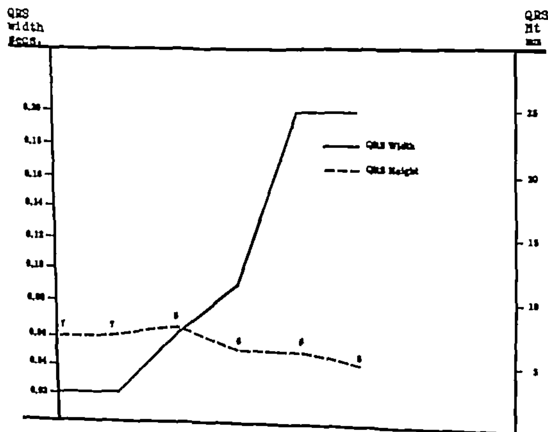
G The same changes are seen to an increased degree

H A terminal ventricular rhythm com

Table I Dog experiment No 1 (male dog weight 5 kilograms)

Dose	Chloroquine base (mg)					
	0	100	200	300	400	500
P Height (mm.) / Duration (mm)	1 5/1	1 5/1 5	1 5/2	2 0/1 5	2 2	2/2
PR duration (mm)	2	2 5	2 5	3	4	4
QRS (sec.)	0 02	0 02	0 06	0 09	0 20	0 70
QRS (mm.)	7	7	8	6	6	5
QT (sec.)	0 21	0 24	—	0 32	0 40	0 40
Rate/min	120	115	140	140	85/mt	85

*1 mm = 0.04 sec.



Graph I Changes in QRS width and height with increasing doses of chloroquine in Experiment No. 1

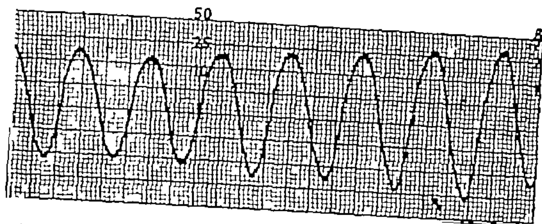


Fig 3 Ventricular tachycardia with broad QRS comple es.

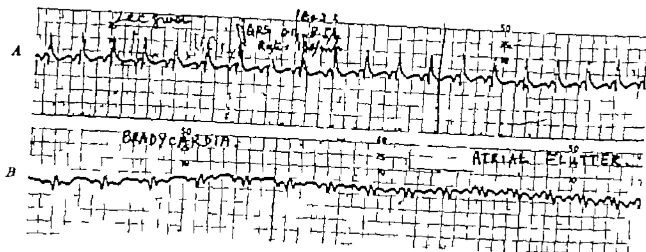


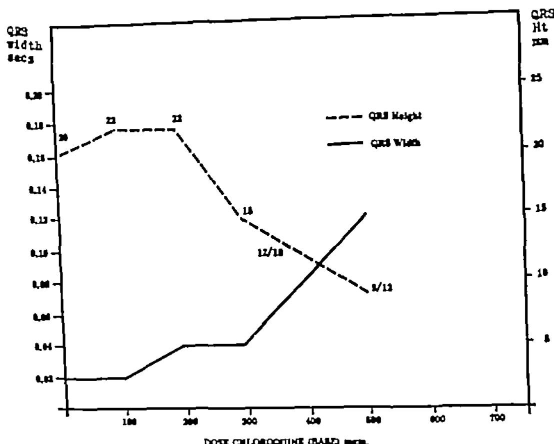
Fig 4 A Bradycardia induced by chloroqu ie. B Bradycardia ltered to tri l fl tter by adrenaline.

mences immediately preceding cardiac arrest.

The changes are summarized in Table III and Graph III The toxic dose was 11 mg per kilogram and the lethal dose 33 mg per kilogram

COMMENT It is to be noted that the systolic pressure and pulse pressure were selectively affected while the diastolic pressure fell much less and was sustained pointing once again to the failure of the heart as a pump Pacing did not restore the pulse indicating that an electrical response does not necessarily produce an effective contraction External cardiac compression however produced both a palpable pulse and a significant aortic pressure The loss of QRS height and its increasing width occurred simultaneously with the fall of aortic pressure At higher doses, an elevation and broadening of the T wave, the summation of P and T with loss of the isoelectric line occurred and were followed by a terminal ventricular rhythm

Experiment 5 A 14 kilogram male dog was used Following the anesthetic respiratory depression occurred and assisted ventilation was given using a Boyle s machine The sequence may be summarized as follows (1) adrenaline 2 c.c. of a 1 1 000 solution induced reflex bradycardia and hypertension (Fig 6 *A*) the rhythm spontaneously reverted to 2 1 atrial flutter (Fig 6 *B*) (2) chloroquine 200 mg (approximately 15 mg per kilogram) was given and atrial flutter reverted to *sinus rhythm* (3) adrenaline, 2 c c administered a second time caused ventricular tachycardia (4) chloroquine 6 c.c. (600 mg) administered up to 8 c c. (800 mg) did not cause cardiac arrest but caused ventricular bradycardia with occasional supraventricular beats



Graph II Changes in QRS width and height with increasing doses of chloroquine in Experiment No. 3

Table II *Dog experiment No 3 (male dog weight 18 kilograms)*

Date	*Chloroquine base (mg.)*					
	0	*100*	*200*	*300*	*400*	*500*
P Height (mm.) / Duration (mm.)	4/1 5	4 5/2	3/2	3/2	3/2.5	2 5/2
PR duration (mm.)	3	3	3	3	3	3
QRS duration (sec.)	0 02	0 02	0 04	0 04	0 08	0 12
QRS height (mm.)	20	22	22	15	12/18	9/12
QT duration (sec.)	0 2	0 18	0 2	0 2	0 28	0 32
Rate/min.	160	160	150	160	150	100

*1 mm. = 0.04 sec

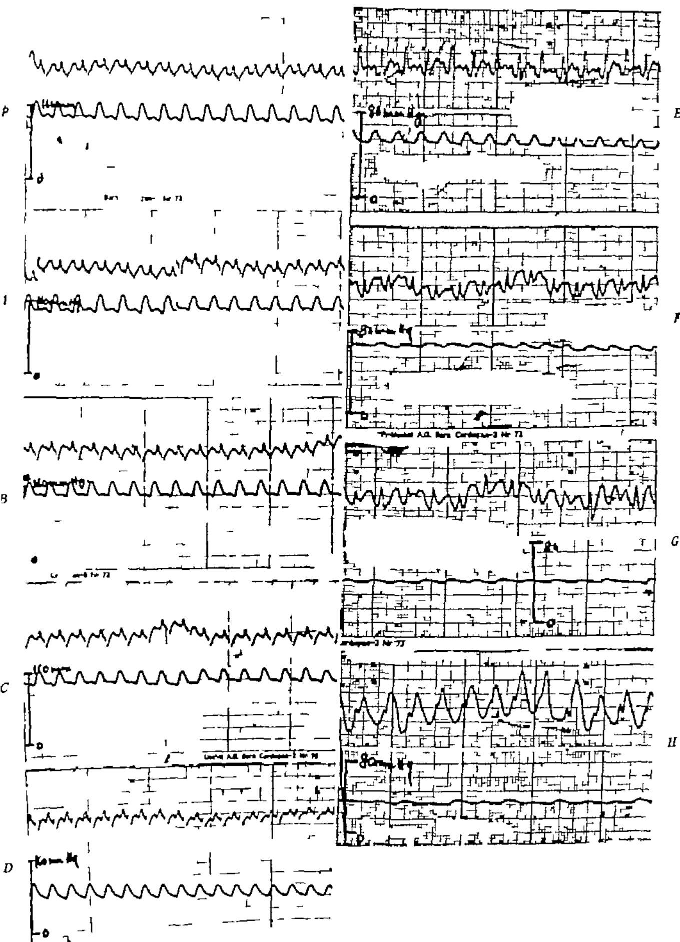


Fig 5 Changes in the electrocardiogram with a simultaneous aortic pressure pulse, during the administration of chloroquine at different dose levels (see text) Top left, *Control*. *A* 100 mg *B* 200 mg *C* 300 mg *D* 350 mg *E* 400 mg *F* 500 mg *G* 600 mg *H* 700 mg

Table III. Relationship between chloroquine dose, blood pressure, and QRS height

Parameter	Dose of chloroquine							
	0	*100 mg*	*200 mg*	*300 mg*	*400 mg*	*500 mg*	*600 mg*	*700 mg*
Systolic BP (mm. Hg)	165	1 0	160	80	95	59	45	0
Diastolic BP (mm. Hg)	128	138	130	58 5	79	49	35	0
Height QRS (mm.)	20	23 5	20	13	9	5	5	15
Duration QRS (sec.)	0 04	0 04	0 04	0 06	0 08	0 08	0 08	0 32
Height P (mm.) / Duration P (mm.)*	2 5/2	2 5/2 5	3/2 5	3/2 5	3 2			
PR duration (mm.)	2 5	3	3	3		—		—
Rate/M.	180	180	180	180	180	—	190	
QT duration (sec.)	0 2	0 2	0 18	0 18	0 2	0 2		—
Rhythm	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus

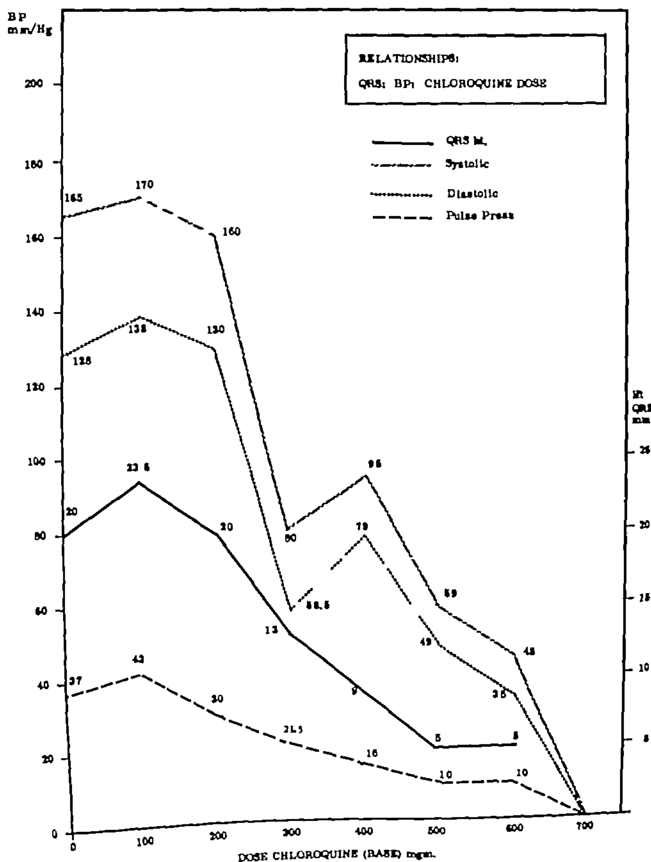
*1 mm. = 0.04 sec.

(5) larger doses (9 c.c.) of chloroquine caused cardiac arrest (the lethal dose was 50 mg. per kilogram). The experiment demonstrates the increased cardiac tolerance of the dog's heart after adrenaline. It also indicates the value of chloroquine as an antiarrhythmic agent.

COMMENT. Certain general conclusions emerge from the animal experiments: (1) Chloroquine appears to be a myocardial depressant drug. (2) adrenaline increases the cardiotoxic dose of the drug and reverses some of its effects on the ECG. (3) hypotension induced by chloroquine is attributable to its myocardial depressant action rather than to vasodilatation. (4) chloroquine is an effective antiarrhythmic agent. (5) the following electrocardiographic changes were observed in sequence: (a) a slight sinus tachycardia, (b) a loss of QRS voltage with or without simultaneous widening of the QRS complex, (c) sinus bradycardia, (d) ventricular tachycardia, (e) ventricular bradycardia, (f) electrical arrest.

Discussion

In the context of acute poisoning, chloroquine may be regarded as a one-way drug. It is completely absorbed from the gastrointestinal tract. About half of the drug is in the plasma bound to nondiffusible constituents. Renal elimination is very slow and increased by urinary acidification. Considerable amounts are deposited in the nucleated cells of the liver, spleen, kidney, lung, and less so in the brain and spinal cord. The nature of its degradation is not fully known and the tissues hold chloroquine for several weeks after it is discontinued. Peak blood levels after a weekly oral dose of 500 mg. are between 150 to 250 mg. per cent. The drug reduces the excitability and conductivity of cardiac muscle but not the velocity of the impulse and is a potent myocardial depressant. This action is not thought to reside in the quinoline ring although the latter is considered as the cause of vasodilatation. At a cellular level it blocks the enzyme succinic dehydrogenase in cells of the conducting system interfering with Krebs cycle. Its acute action on the cardiovascular system has been poorly documented but it is a known antiarrhythmic agent[4] and has been used in the treatment of angina pectoris in humans. It is recognized as causing hypotension which was attributed to peripheral vasodilatation,[5] although the author appears to contradict this conclusion by emphasizing the



Graph *III* Changes in the QRS height, blood pressure, and pulse pressure with increasing doses of chloroquine in Experiment No. 4

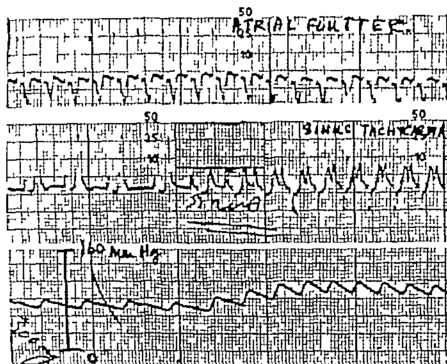


Fig. 6 Atrial flutter *A* Induced by adrenaline. *B*, Reverted to sinus tachycardia by chloroquine

maintenance of diastolic pressure while the systolic pressure drops.

The effects on the ECG in acute poisoning have not been previously documented in a human case of poisoning although the effects of administering the drug for 1 to 21 days have been described. These effects consisted of inversion of the T wave in the precordial leads, S-T segment depression and QT prolongation and they were reversed by the administration of potassium

Deaths from chloroquine poisoning have only recently been described The first published English report of four cases was in 1961 although more cases have been described since then [8]. The French literature however has earlier reports of poisoning.[11]

The mechanism of death from chloroquine ingestion would appear to be related to a failure of myocardial contraction, aggravated by bradycardia and the appearance of ventricular rhythm in the terminal stages rather than to respiratory or vasomotor depression. Antidotal therapy with adrenaline and atropine was highly effective in our patient (Patient 1) who sustained cardiac arrest. Considering the reversal of cardiac arrest by adrenaline, it is interesting to speculate on whether pretreatment with sympathomimetic agents and atropine would protect against chloroquine toxicity This may provide a means of preventing sudden death in predisposed persons. It is regrettable that some currently available schedules for the treatment of malaria are based on age[14] and not on weight. This is especially a problem in less developed countries. Using 5 to 14 mg per kilogram of chloroquine base intravenously [15] there were no side effects encountered in patients infected with falciparum malaria. Drug schedules based on weight would thus seem to be the more rational method This would possibly have prevented the death recorded (Patient 2) Since the drug is rapidly absorbed and slowly excreted it would be a good working rule not to exceed 14 mg. per kilogram orally with special care taken in patients whose excretion is impaired.

While it is submitted that the drug has

had widespread use for the past two decades and toxicity would appear to be rare it must be accepted that drug idiosyncrasy similar to that due to quinidine and genuine toxicity due to overdosage need to be borne in mind whenever the drug is used The use of a small preliminary dose of chloroquine similar to quinidine however does not seem practical

Chloroquine is a powerful cardiotoxin and should be stored in containers labelled poison Its widespread use in malarial areas has increased its availability and correspondingly reduced the degree of medical supervision accompanying its administration This is strongly deprecated as are suggestions to add chloroquine to common salt.[16] It is urged that when chloroquine is used in large doses, it is given inside a hospital with full precautions taken Patients with heart disease and those receiving large doses with renal disease and alkalosis need to have their blood pressures and electrocardiograms recorded before and a few hours after receiving the drug During treatment they should remain at rest.

Summary

The cardiovascular effects of acute chloroquine intoxication have been described in three patients and in five animal experiments The drug appears to act as a potent myocardial poison reducing the output of the heart and causing disturbances of conduction bradycardia and arrhythmias As far as we know the first two human cases ever which illustrate the electrocardiographic changes induced by acute chloroquine poisoning are the ones presented (Patients 1 and 3) The sequence of changes in the electrocardiogram in acute poisoning in dogs is described Adrenaline was found to be an effective antidote as well as a preventive drug Appropriate precautions are suggested to prevent the occurrence of accidental death or induced poisoning These emphasize the administration of the drug on a weight rather than an age basis. The use of small doses similar to quinidine may prevent drug idiosyncrasy but does not seem to be practical Considering the widespread use of chloroquine and its increasing administration it is necessary to consider the precautionary measures outlined on an international scale.

My thanks are due to my colleagues, Drs. Galoostian, Koochek, Bet Badal, Farshid and Vasefi, and to Miss Izazadeh. My thanks are also due to Dr Nakjlv n for permission to quote from his case reports. I am indebted to Mrs. A. Lambert for her assiduous secretarial assistance and to Messrs. B nesh and Chehrehnegar for preparing the illustrations. Finally I am indebted to the National Iranian Oil Company for permission to publish this paper

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Treatment of cardiac failure with glucagon

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The hormone glucagon, a secretory product of the alpha cells of the pancreas, possesses a wide range of physiologic and pharmacologic effects on carbohydrate, lipid, and electrolyte metabolism. Its most important action, and the one which has been used in clinical therapeutics, is increasing blood glucose concentration by stimulating hepatic glycogenolysis. While cardiovascular actions of glucagon were identified about ten years ago, it has been only in the past two or three years that more intensive investigation of this aspect of the pharmacology of glucagon has been undertaken. It is the purpose of this report to summarize briefly the results of these studies and their therapeutic implications.

In several types of experimental preparations *glucagon has been shown to have a* significant positive inotropic effect. Maximum developed tension and velocity of fiber shortening of the isolated papillary muscle are increased, stroke volume in the heart-lung model is increased, maximum rates of rise of ventricular pressure and force developed in the intact dog are increased. Augmentation of contractility is not abolished by reserpine or propranolol, indicating the action of glucagon is not mediated by catecholamines or beta adrenergic receptors. In addition, the inotropic effect occurs after administration of ouabain.

Animal studies have also demonstrated important effects of glucagon on impulse transmission and formation. The rate of automatic pacemakers in the sinoatrial node and atrioventricular junction is increased. Idioventricular pacemakers are not accelerated. The duration of the functional refractory period of the A-V junction is decreased and the speed of impulse transmission across the A-V junction is increased. Propranolol-induced A-V conduction delay is abolished by glucagon. Beta adrenergic receptor blockade does not alter the positive chronotropic effect on the sinoatrial node except when small doses of glucagon are employed. Ectopic rhythms are not induced. When extrasystolic and automatic impulses of ventricular origin are evoked by *experimental myocardial infarction,* glucagon does not increase their frequency.

The mechanisms responsible for the inotropic effect of glucagon are unknown. The original suggestion that *catecholamine* release and beta-adrenergic receptor stimulation play a role has been generally discarded. Whether the adenyl cyclase, cyclic adenosine monophosphate system is involved is uncertain. Prevention of hyperglycemia by pretreatment with insulin does not prevent the enhanced contractile response nor does vagotomy.

Hemodynamic observations in man have confirmed the positive inotropic effect of

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glucagon Several dose schedules have been tested 3 to 5 mg given over a one-minute period 2 to 3 mg per minute for 10 to 15 minutes to a total of 20 to 45 mg 2 to 4 mg per hour for 10 to 13 days In most of the subjects studied significant increases in cardiac index (13 to 40 per cent) and left ventricular dp/dt were noted Responses were usually observed in 5 minutes, with the peak at 15 minutes and dissipation of effect within 30 minutes. Stroke work stroke power and mean ejection rate also increased although less consistently than cardiac output and the rate of pressure rise in the ventricle Some investigators have reported a slight fall in left ventricular and diastolic pressure others have reported no change Similarly the effects of glucagon on systemic vascular resistance and arterial pressure have been minor and inconstant. A modest transient increase in heart rate occurred in most subjects.

In the studies cited no major side reactions were noted Nausea occurred frequently with a 5 mg dose and nausea with vomiting occurred in all patients who received as much as 20 to 45 mg over a 10 to 15 minute period Small doses (2 to 4 mg per hour) did not cause nausea A reduction in plasma potassium concentration usually less than 1 mEq per liter occurred in almost all subjects receiving 3 to 5 mg of glucagon However cardiac arrhythmias were not observed even in patients receiving digitalis

The special properties of glucagon enhancement of contractility without initiation of ectopic rhythms or excessive acceleration of supraventricular pacemakers or depression of A V conduction may make this substance a useful addition to the list of inotropic agents currently available for the treatment of cardiac failure It may be of value in the short term management of patients in whom the dose of digitalis must be restricted because of cardiac arrhythmias It may be of value as an addition to digitalis in patients who are in the refractory phase of cardiac failure. It may be of value in patients with acute cardiac failure due to myocardial infarction in whom the hazard of arrhythmias may contraindicate the use of digitalis. It may be an effective substitute for or addition to isoproterenol in certain states While these and other potential indications for the use of glucagon exist only a few observations as to its actual clinical effectiveness have been reported A group of four patients in congestive heart failure who did not respond to conventional therapy appeared to manifest significant improvement after receiving continuous infusions of glucagon for 10 to 13 days In the low output state following cardiac surgery glucagon increased cardiac index stroke work index and systolic ejection rate

The unique pharmacologic actions of glucagon on the cardiovascular system and the preliminary experiences already reported justify the suggestion that a systematic survey of the range of its clinical usefulness is indicated

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Annotations

The use of quinidine with fixed rate pacemakers*

Because of the frequent occurrence of arrhythmias in patients with artificial cardiac pacemakers, antiarrhythmic drugs such as quinidine may be indicated. However Rothfeld and associates recently cautioned against the use of quinidine in patients with competition between fixed-rate pacemakers and either normal or ectopic spontaneous rhythms because of their observation of ventricular tachyarrhythmias in 14 of 20 dogs with similar pacemaker competition. These repetitive rhythms were initiated by pacemaker stimuli occurring in the vulnerable period after the administration of quinidine, but not during control periods.

In order to confirm these observations, we studied 17 mongrel dogs, using essentially the same protocol except for the anesthesia as described in the report of the Rothfeld group. Fifteen dogs were anesthetized with a mixture of chloralose and urethane and two with sodium pentobarbital. Temporary fixed-rate pacing was initiated after a bipolar catheter was passed via the external jugular vein into the right ventricle. A stable state with competition 50 per cent of the time was attained by adjusting the pacemaker rate. After a 15 minute control period quinidine was administered intravenously in a dose of 5 mg. per kilogram. Twelve dogs received three doses over a 30 minute period while 5 dogs received a single injection. Continuous electrocardiographic monitoring for 30 minutes failed to reveal any episode of ventricular tachycardia or fibrillation and there were no fatalities.

The disparity between these results and those of Rothfeld and co-workers could not be explained but it should be noted that in the latter study pentobarbital was used as an anesthetic whereas in this study chloralose-urethane was employed in all but 2 dogs. On the basis of these findings, there does not seem to be any contraindication to the use of quinidine in patients with fixed-rate pacemakers and competitive rhythms.

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Digitalis-induced cardiac arrhythmias

Digitalis is an indispensable drug in the treatment of congestive heart failure and most supraventricular tachyarrhythmias, but it may cause or aggravate the congestive heart failure or serious cardiac arrhythmias if the patient develops digitalis intoxication. Although such gastrointestinal symptoms as anorexia, nausea, and vomiting have been said to be the most common early symptoms, arrhythmias may often indicate digitalis toxicity without such signs. The occurrence of arrhythmias is particularly common and is frequently the only sign of digitalis intoxication when using purified preparations. It is a well-known fact that digitalis may produce every known type of cardiac arrhythmia via an alteration of impulse formation, conduction, or both. It is commonly observed that patients with

*Table 1 Incidences of digitalis induced cardiac arrhythmias**

Rhythm	Herrmann[2] 1944 (44)	Flaxman[3] 1948 (30)	Crouch[4] 1956 (80)	Shrager[5] 1957 (40)	Von Capeller[6] 1959 (141)	Rodensky 1961 (58)	Dreifus[8] 1963 (161)	Dubnow[9] 1965 (61)	Chung 1968 (180)	Total [%] (726)
Sinus bradycardia	2	4	—	—	5	—	4	—	10	25 [3 4]
Sinus arrhythmia	—	—	—	—	—	—	—	—	5	5
Sinus tachycardia	—	—	16	2	12	—	—	—	7	37 [5 1]
S-A block	—	—	—	—	—	—	—	—	4	4
Sinus arrest		2	—	—	9	—	—	—	2	13 [1 8]
Atrial tachycardia	20	—	7	1	13	9	23	8	19	102 [14 1]
Atrial fibrillation	10	10	19	3	27	—	—	—	3	72 [10 0]
Atrial flutter		—	4	3	3	—	—	—	3	13 [1 8]
A.P C	—	—	16	4	7	—	—	3	25	55 [7 6]
W.A.P		—	3	2	6	—	—	5	3	19 [2 6]
A V nodal tachycardia	—	—	—	—	8	8	74	—	44	134 [18 5]
A V N.E.R.	—	—	—	5	8	—	—	17	39	69 [9 5]
A V dissociation		—	9	1	—	25	—	17	75	127 [17 5]
N.P C.	—	—	—	—	4	—	—	—	5	9
1° A V block		4	10	13	36	17	—	—	22	102 [14 1]
2° A V block	7	3	7	6	19	8	3	31	36	122 [16 8]
3° A V block			14	4	9	5	43	—	6	81 [11 2]
V.P C	18	11	65	18	108	30	—	58	83	391 [53 9]
Bigeminy	12	6	34	10	49	15	—	30	28	184 [25 4]
Multifocal					83		—	17	30	132 [18 0]
Ventricular tachycardia		1	13	1	17	4	30	4	16	86 [11 9]
Ventricular fibrillation		—	3	—	1	3	—	1	2	10 [1 4]
Idioventricular rhythm	—	—	—	—	—	—	—	—	1	1

Abbreviations A.P C Atrial premature contraction W.A P wandering atrial pacemaker; N E.R., nodal escape rhythm; N.P C nodal premature contraction V P C ventricular premature contraction

*Total patients in each study indicated in parentheses

digitalis intoxication demonstrate various combinations of arrhythmias. Arrhythmias may change from one to another in the same electrocardiographic tracing. In general cardiac arrhythmias occur in 80 to 90 per cent of patients presenting with digitalis intoxication.

The purpose of this paper is to review the previous literature concerning digitalis intoxication with particular emphasis placed on the importance of early recognition of digitalis-induced arrhythmias especially A V nodal arrhythmias in the presence of atrial fibrillation. One hundred and eighty cases of digitalis intoxication are included for discussion. The incidences of various digitalis-induced arrhythmias studied at nine different institutions[2-9] are shown in Table 1. A precise comparison between this author's study and that of others is unfortunately impossible since most authors failed to describe various arrhythmias.

Among 180 cases of the present study 102 were men and 78 patients were women. The ages ranged between 20 and 95 years. One hundred and twenty seven patients had two or more different arrhythmias. The total incidence of digitalis induced arrhythmias was 346 episodes in 180 patients. As can be expected every known type of cardiac arrhythmia was encountered. The basic rhythm was atrial fibrillation in 87 patients and almost all of these patients (83 patients 46 per cent) showed either nonparoxysmal A-V nodal tachycardia (Fig 1) or A V nodal escape rhythm induced by digitalis (Table 1). This information is extremely important since A V nodal arrhythmias in the presence of atrial fibrillation are frequently misinterpreted as uncomplicated atrial fibrillation.[3-4] Continued administration of digitalis would lead to irreversible congestive heart failure or even death under these circumstances. In this study atrial fibrillation and flutter were each found in only 3 patients. It is quite interesting to note that atrial fibrillation or flutter which were both very rare digitalis-induced arrhythmias, have been reported by different investigators as relatively common arrhythmias in digitalis toxicity[3-4] (Table 1). This is usually due to misinterpreting A V nodal arrhythmias in the presence of atrial fibrillation. Nineteen patients (10.6 per cent) had atrial tachycardia, but in the majority (12 patients) of these patients, it was associated with A V block. One interesting observation in this study was a relatively high incidence (11 patients) of blocked (nonconducted) atrial premature contractions (Fig 2). The author

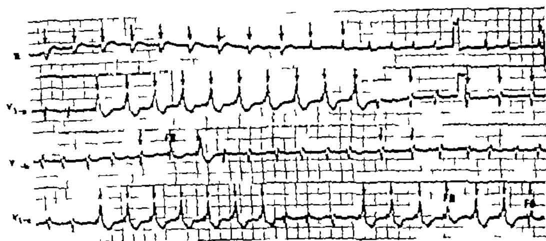


Fig. 1. Leads V... V..., and V... are continuous. The rhythm is atrial fibrillation and there is intermittent A-V nodal tachycardia (ventricular rate 120 per minute) with intermittent aberrant ventricular conduction producing incomplete A-V dissociation. Arrows indicate the QRS complexes in A-V nodal tachycardia. *FB* designates fusion beats.

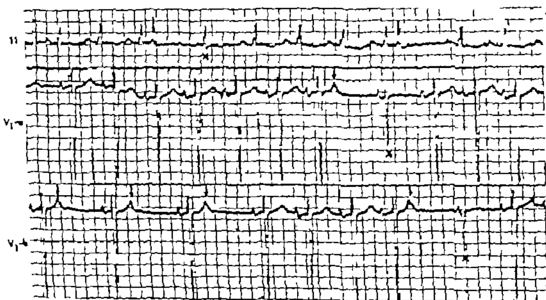


Fig. 2. Leads V... and V... are continuous. The basic rhythm is sinus with first degree A-V block (P-R interval 0. 3 second). There are frequent nonconducted atrial premature contractions (indicated by arrows) followed by occasional A-V nodal escape beats (marked *X*). It is interesting to note that all of the A-V nodal escape beats show aberrant ventricular conduction.

believes that the frequent occurrence of nonconducted atrial premature contractions is an almost pathognomonic sign of digitalis toxicity during digitalis therapy. Disturbances of sinus impulse formation and conduction were found only in 28 subjects (15.6 per cent). A-V conduction disturbances in various degrees were encountered in 64 patients (35.6 per cent). Second degree A-V block ... the most common (36 patients) form noted. Only 6 patients had complete A-V block in the presence of sinus mechanism in the atria, whereas 35 patients showed complete or advanced A-V block in the presence of atrial fibrillation. First degree A-V block was seen in 22 subjects (12.2 per cent). The over-all incidence of ventricular arrhythmias was highest (104 patients, 57.8 per cent)

in this study and among these arrhythmias ventricular premature beats predominated (85 patients: 47.3 per cent). The incidence of ventricular bigeminy (28 patients) and *multifocal ventricular premature* beats (30 patients) was almost equal. Ventricular tachycardia was found in 16 patients (8.9 per cent) and 2 of them had bidirectional ventricular tachycardia. Two patients had ventricular fibrillation and both died. A *total of 38* patients died of *intractable* heart failure and/or irreversible cardiac arrhythmias. In treating mild cases of digitalis intoxication discontinuation of the drug alone was satisfactorily effective. However if intoxication was *manifested by frequent* premature beats or tachyarrhythmias, potassium or Dilantin (diphenylhydantoin) was administered, *in addition to omit*ting digitalis. Potassium was highly effective even in the presence of a normal serum *potassium value*. *In urgent situations*, an intravenous infusion of potassium or Dilantin was carried out. Potassium and *Dilantin* were equally effective *in treating* digitalis-induced supraventricular *tachyarrhythmias* whereas the latter was more effective *in treating* ventricular arrhythmias. Xylocaine was administered to 6 patients for the treatment of ventricular arrhythmias with various success. A temporary artificial pacemaker was used with good results in 2 patients for complete A V block.

A *recognition of digitalis-induced* cardiac arrhythmias, particularly A V nodal arrhythmias *in* the presence of atrial fibrillation, is extremely important because cardiac arrhythmias may often indicate digitalis intoxication without any other signs. Sudden appearance of rapid or slow heart action during digitalization should make one suspect of digitalis toxicity rather than the need for increased digitalis. There is an appreciable mortality rate in patients with digitalis-induced arrhythmias, particularly if they *go unrecognized*. *Immediate* recognition of digitalis toxicity and withdrawal of digitalis are *essential* to minimize the relatively high mortality rate.

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Of the United States Government, history taking, and the physical examination

It is well known that it is impossible to place satisfactorily monetary values on *professional medical* services. Nevertheless it is attempted even by the United States Government. Unfortunately remunerations for services often dictate the quality and type of services rendered patients. Through its Medicare and Medicaid programs, the United States Government does have an *opportunity to* influence the quality and type of medical practice through its remuneration for services. The fact apparently has not been fully appreciated. Senator Warren Magnuson is aware of this and in a statement before the Subcommittee on Executive Reorganization of the Committee on Government Operations has expressed himself clearly. To quote:

> Basic to a consideration of medical care costs is the professional fee structure of medicine. I suggest that the fee structure is unsound and in itself contributes to excessive costs. Fee structures are heavily weighted toward encouraging procedures rather than time and skill. Surgically oriented third party fee structures are the

norm doing something to patient pays, talking with him does not. A doctor can receive $25.00 for taking 5 minutes to sew up a cut, but would be considered daring to charge $12.50 for a half hour counselling session. This inequality may force many physicians to perform procedures which others are better qualified to do. The quality of medicine could be improved, at lower cost to the public, were physicians adequately compensated for their time and skill rather than for procedures. Reform of the fee schedules in federally sponsored programs, in cooperation with the medical profession, would be one place *to start*."*

Further emphasis of the importance of our Government role in such matters is indicated by the values accepted by the Social Security Administration *for services and procedures* under the Medicare program. For example, a doctor can earn more money by *ordering* a vectorcardiogram ($50.00), which has little established clinical value and requires no *time* of his own, than he receives for an office or clinic visit ($6.00) which should and usually does require a great deal of his own time for talking to his patient, carefully examining him, and counselling him, the most important of all aspects of good practice. A review of the list of accepted charges displays many and even more glaring examples of inappropriate emphasis on values by monetary evaluations.

Recognizing human nature, it requires very little imagination to realize the response of physicians in practice to the Government attempt to set the fees for their services with such a sense of values.

The master clinician finds such action by the Government impossible to understand. Perhaps it is such establishment *of unrealistic* monetary values on the practice of medicine that so inhibits and discourages good medical practice. This type of action may contribute to reducing the effectiveness of medical practice to such an extent *that the life* and health insurance companies need not impose extra premiums on Christian Scientists nor reject them for life insurance even though they do not "benefit from medical practice. Apparently the *life* expectancy of Christian Scientists is not significantly different from non-Christian Scientists who employ physicians. Such facts reveal major deficiencies in medical education, emphasis in time and fees for services which influence the quality of practice, lay and professional. It is no wonder that history taking, physical examinations, and time with patients and their families are so blatantly neglected when even our Government values them *so little*.

Fees approved by the Social Security Administration for Medicare claims are

Office visit	$ 7.00
Vectorcardiogram	35.00
Phonocardiogram	35.00
Cardiac catheterization	471.00
Coronary angiocardiography	140.00
Gastroscopy with gastrophotography	125.00
Peroral jejunal or gastric biopsy	150.00

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*The Internist 9:1 (December), 1968.

A cardiac vector indicator

The cardiac vector *indicator* described below has been developed in connection with implanted cardiac pacemaker investigations but its wider use is also envisaged.

One of the basic postulates of electrocardiography is that all the electrical forces of the heart can be summed at any instant to give a single resultant force, which can be represented in magnitude and direction by a vector. Similarly the electrical pulse generated by an implanted cardiac pacemaker can be represented by a single vector. Studies on the frontal plane projection of this vector have already been reported. Vectorcardiography can be used to obtain the projections of the pacemaker vector on three planes, frontal, sagittal, and transverse.

The indicator however provides not only planar display but enables the vector to be viewed *in three dimensions*.

The indicator (Fig. 1) consists *essentially of three* intersecting transparent perspex sheets placed mutually at right angles *to one another to correspond* with the frontal, sagittal, and transverse planes. A disc of perspex is removed *from the center of each* of the planes and another smaller disc is mounted in the space thus *formed. A movable* pointer which is spring-loaded and mounted radially in the plane of this disc, can be *orientated into* almost any position. The pointer cannot lie in any of the three planes occupied by the thin perspex sheets, but since the minimum deviation from these planes is



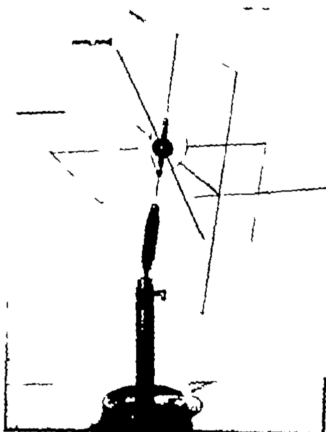


Fig 1 General view of cardiac vector indicator

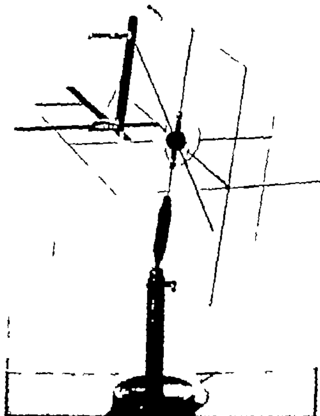


Fig 2 General view of cardiac vector indicator showing measuring jig in use.

quite small in practice this limitation is of no importance The effective length of the pointer can be changed by retracting the tip toward the origin of the system The indicator is mounted on a stand fitted with a universal coupling for the convenience of the user to enable any one of the three planes to be viewed normally i.e face on

A measuring jig (Fig 2) is used to assist positioning of the pointer It consists of three arms fixed mutually at right angles to one another two of the arms are of adjustable length while the third is calibrated only The three leads of a vectorcardiogram (in our case derived from the modified axial system[2]) record the component voltages of the pacemaker vector The arms of the jig are adjusted to correspond to two of the measured voltages before it is positioned on the indicator The pointer is then orientated until its tip touches a point on the fixed scale corresponding to the third measured voltage The measuring jig is then removed from the indicator The frontal plane pacemaker vector can be readily observed in relative magnitude and position by viewing the pointer normal to the frontal plane In a similar fashion the transverse plane and sagittal plane projections of the pacemaker vector can be seen

The indicator can be used with any set of orthogonal axes, the *only* prerequisite being that the user must decide the appropriate orientation of the vector

Aside from pacemaker vectorcardiography the indicator should prove extremely useful as a teaching aid for electrocardiography since the electrical activity of the heart is of a three-dimensional nature It should help students visualize the transition from three-dimensional reality to two-dimensional clinical techniques

We should like to thank Mr E. I F bes and Mr W Hyslop (of the Regional Department of Clinical Physics and Bio-Engineering) who helped to finalize the design and who were also responsible for the construction of the indicator

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BIOCHEMISTRY OF THE VASCULAR WALL (Part I). Proceedings of International Symposium held in Fribourg, June 21 and 22, 1968, Basel and New York, 1969, S. Karger AG, 196 pages. Price $19.20.

The proceedings of an international symposium held in Fribourg, Switzerland, June 21 and 22, 1968, are summarized in this publication. The contributors are mainly European and the subjects discussed rather broad. They included studies of the following components of the vascular wall: collagen, ions, mucopolysaccharides, lipids, carbohydrates, proteins, myosin, and elastin among others. The attention was directed primarily toward atherosclerosis. This is a good review in one volume of several important aspects of vascular biochemistry. Important as the symposium was, it brought us no closer to knowing why or how atherosclerosis develops or how to prevent it. This is a good monograph presented in a conventional fashion.

CORONARY HEART DISEASE. Edited by Albert N. Brest, M.D. Philadelphia, 1969, F. A. Davis Company, 325 pages. Price $8.00.

This is the second publication in the *Cardiovascular Clinics* series. The first was "Hypertensive Cardiovascular Disease" and the next will be "Cardiovascular Therapy." There are many brief presentations of many subjects related to coronary heart disease. These presentations are, as would be expected, reflections of the opinions of the contributors. The reader must know the authors in order to evaluate the statements made. For example, on page 137 a contributor states, "The general impression is that vectorcardiograms are more accurate than electrocardiograms. When recorded properly and with good fidelity apparatus, both recordings are accurate. Now if he refers to diagnosis, it is necessary to qualify the statement considerably. For example, the measurement of P-R or other intervals or the diagnosis of cardiac arrhythmias is certainly much more accurate when obtained from electrocardiograms than from vectorcardiograms.

This publication resembles in format the *Medical Clinics of North America* and should serve the same purpose. The reader must also determine for himself if he is convinced that coronary care units, special coronary care vehicles or ambulances, and presently operated coronary angiography including other new practices, as well as drugs, apparatus, etc. are yet sufficiently evaluated or established for his own convictions and use in his practice. These presentations must be read with considerable thought and caution. The presentation is not a critical one.

DIGITALIS. Edited by Charles Fisch and Borys Surawicz, New York, 1969, Grune & Stratton, 230 pages. Price $14.75.

This is a very good book on an important and commonly used drug. Digitalis is not as well known to the practicing physician as it should be. There is too great a habit of using the drug without knowing its actions or how to regulate the dosage precisely. This is even more so today with the use of diuretics and other vasoactive and cardiac agents. This monograph very well summarizes aspects of chemistry and metabolism of digitalis, effects on ion fluxes and cardiac contractility, electrophysiologic aspects, and clinical use. The book is clearly written and sufficiently complete for medical students, interns, residents and practicing physicians. The many contributors are investigators who have been studying the effects of digitalis on the heart. Their presentations are important even for the clinician who often wishes to know more about the details of action of digitalis. Some discussions are rather technical for those in practice, but worth knowing. Unfortunately for the doctor in practice, there were not more clinical aspects of the drug included. This is an authoritative monograph and is highly recommended.

CARDIOVASCULAR SURGERY. Current Practice, Volume I. Edited by Thomas H. Burford and Thomas B. Ferguson, St. Louis, 1969, The C. V. Mosby Company, 273 pages. Price $18.00.

This volume on cardiovascular surgery is intended for beginners in cardiovascular surgery. The editors and contributors correlate technique with physiology and surgical practice. The subjects discussed include whole body perfusion with the heart-lung machines, postoperative care of the patient after open-heart surgery, tetralogy of Fallot, artificial valves, myocardial revascularization, cardiac transplantation, and ventricular assist devices. Thus, these selected topics are important subjects but they do not cover the entire field of cardiovascular surgery. Since this is Volume I, the editors must intend to discuss many other subjects in the subsequent volumes.

The discussions are good, though brief. The illustrations are clear and well selected. This book should be of interest to students, interns, residents, and surgeons. Each chapter is appended with a good bibliography. This volume is highly recommended. However, it is only through direct experience and patient responsibility that one can become an accomplished cardiovascular surgeon. This book can serve the beginner as a background for practical experience. Those who are

not cardiovascular surgeons will also find Volume I to be informative.

THE MOMENT OF DEATH A Symposium. Edited by Arthur Winter M D Springfield Ill. 1969 Charles C Thomas, Publisher 84 pages. Price $6 00.

This small book (84 pages including the appendix and index) should interest all doctors, lawyers legislators, medical examiners and others concerned with death It is obvious that this book edited by a neurosurgeon who conducted a symposium on death on Sept 18, 1968 is in response to the discussions stimulated by cardiac transplantation. The six contributors, a medical examiner Attorney General, two neurosurgeons, and an emeritus professor of medicine express their opinions concerning the medical-legal aspects of death and who when, and how the pronouncement of death is to be made The definition of death is discussed All of the papers are interesting and the subject is important, but this short monograph fails to satisfy the needs for the entire United States or the world. This reviewer realizes the definition of death is difficult from the point of view of donor hearts for transplantation, but unless more interest is shown by clinicians and scientists in the many related problems, the legal and legislative professions will define it by law They are human and not infallible.

MEASUREMENT IN EXERCISE ELECTROCARDIOGRAPHY Edited by Henry Blackburn, M D Springfield, Ill., 1969 Charles C Thomas, Publisher 488 pages. Price $21 00.

This Ernst Simonson Conference, held on Sept. 28 and 29 1967 at the Minneapolis Veterans Administration Hospital, in honor of a very fine man who made important contributions to electrocardiography should interest all cardiologists. The monograph reviews the thoughts of the contributors about an important electrocardiographic concept in research and the practice of clinical cardiology The symposium was divided into six parts dealing with electrical and physiological background methods and computer programming bioengineering, conceptual and procedural problems, variability and human experiments, and diagnostic reliability Each part contains several papers and many discussions. The informal discussions constitute one of the most interesting and informative aspects of the book. This is a good compendium on an important subject. However from the practicing physician's point of view the value of the exercise electrocardiogram remains of some but limited, value for the present time The book is useful for those interested in investigations of the subject. It is a good review of certain aspects of exercise electrocardiography and should be read by cardiologists and investigators concerned with exercise and with electrocardiography

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